IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	LOCALIZED DELIVERY TO A TARGET SURFACE
WILLIAM R. WAGNER et al.	:	Art Unit 1633
Application Number 09/894,547	:	Examiner Ileana Popa
Filing Date: June 28, 2001	:	Attorney Docket Number 214001-00810-1

DECLARATION UNDER 37 C.F.R. § 1.132

Eckert Seamans Cherin & Mellott, LLC
U.S. Steel Tower
600 Grant Street, 44th Floor
Pittsburgh, Pennsylvania 15219

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, William R. Wagner, declare as follows:

1. I am one of the named inventors of the invention described and claimed in the above-identified patent application.

2. I am a citizen of the United States and reside at 10193 Sudberry Drive, Wexford, PA 15090. I attended The Johns Hopkins University from 1982-1986 and graduated with a B.S. in chemical engineering. I attended The University of Texas at Austin from 1986-1991 and graduated with a Ph.D in Chemical Engineering. From September, 1986 to March, 1991, I was a research associate in the Department of Chemical Engineering at The University of Texas at Austin; from September, 1996 to June 1999, I was a member of the core faculty in the Department/Program of Bioengineering at the University of Pittsburgh, an Assistant Professor of Chemical Engineering in the Department of Chemical Engineering at the University of Pittsburgh and an Assistant Professor of Surgery in the Department of Surgery at the University of Pittsburgh; from July, 1999 to December 2006, I was an Associate Professor of Bioengineering and Chemical Engineering in the Departments of Bioengineering and Chemical Engineering at the University of Pittsburgh, an Associate Professor of Surgery (tenured) in the Department of Surgery at the University of Pittsburgh. I

have served as a Deputy Director of the McGowan Institute for Regenerative Medicine at the University of Pittsburgh since 2001 and have been a Professor of Surgery, Bioengineering and Chemical Engineering at the University of Pittsburgh since December 2006. A copy of my curriculum vitae is attached hereto as Exhibit A.

3. I have read and am thoroughly familiar with the contents of the above-identified patent application as well as the contents of the Office Action dated August 8, 2006. As a specialist in the field of biomedical engineering, and on the basis of this review, it is my well-considered opinion that one skilled in the art would not require undue experimentation to practice the claimed method of the present invention. Specifically, I can attest that not only would one skilled in the art be able to practice the claimed invention with respect to a two-step delivery of a chemical or biological entity to an *in vitro* or *in situ* isolated vascular tissue, but also would be able to practice the claimed method with respect to delivering a chemical or biological entity to any target tissue or cellular surface of a patient *in vivo*. Evidence for these attestations is provided below.

4. As fully described in a paper written by the inventors, entitled "In Vivo PEG-Modification of Vascular Surfaces for Targeted Delivery (attached hereto as Exhibit B), an investigation was conducted involving the *in vivo* PEG-modification of vascular surfaces for targeted delivery of microspheres as models of chemical and biological entities. The study involved employing a protein-reactive polymer to modify injured vascular surfaces for the purpose of blocking thrombosis and providing a site for the targeted delivery of therapeutics as a means of preventing restenosis. N-hydroxysuccinimide-polyethylene glycol biotin (NHS-PEG biotin) was used to covalently modify vascular surfaces in an *in vivo* rabbit femoral artery model of vascular injury. The NHS reactive group covalently linked with primary amines, with the most accessible being the epsilon amine found on the amino acid lysine. A stable amide bond was formed, covalently linking the protein-reactive polymer with the lysine residue of a protein on a vascular surface.

5. The established protocol and results of the investigation are provided in Exhibit B at pages 5-16. Briefly, the above-described investigation showed that NeutrAvidin-coated microspheres preferentially adhered to balloon-injured arteries modified with PEG-biotin as opposed to balloon-injured, unmodified vascular surfaces *in vivo* at all time points evaluated. Microspheres are representative of a particulate drug or carrier that can be loaded with various therapeutics designed to treat various ailments in a patient.

6. The investigation also evaluated the ability of using the same targeting strategy to target agents to healthy vascular tissue, which could be employed to deliver

chemotherapeutics to tumor vasculature, in addition to the targeting of pharmaceuticals to sites of vascular injury. The study revealed that, as was the case with targeting balloon-injured arteries, the NeutrAvidin-coated microspheres preferentially targeted healthy vascular tissue that was modified with polymer as opposed to unmodified arterics.

7. I declare that, contrary to the Examiner's assertions contained at pages 5-6 of the August 8, 2006 Office Action, the above-described investigation clearly demonstrates the ability to provide site-specific recognition signals for delivery of chemical and biological entities, as claimed in independent claim 1, to healthy and damaged tissues. Furthermore, the investigation also demonstrates that chemical and biological entities can be delivered to healthy and damaged tissues without encountering problems with endogenous biotin blocking the biotin-binding sites of streptavidin.

8. In conclusion, the results of this investigation clearly demonstrate that healthy and injured vascular segments can be modified *in vivo* in a patient. Furthermore, as one skilled in the art confronted with the disclosure of the instant application, I would unquestionably be able to practice the claimed invention, as would others who are skilled in the art, as set forth in claims 1-3, 5, 7-12, 19, 24 and 26-28, without undue experimentation.

9. I declare further that all statements made herein of my own knowledge are true and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application and any patent issuing thereon.

(NAME)

1/26/07

(DATE)

CURRICULUM VITAE

BIOGRAPHICAL

Name: William R. Wagner

Birth Date: May 29, 1964

Home Address: 10193 Sudberry Dr.
Wexford, PA 15090

Birth Place: Phoenix, AZ

Citizenship: U.S.

Mobile Phone: (412) 352-1679

Business Address: McGowan Institute for Regenerative Medicine
University of Pittsburgh
100 Technology Dr.
Pittsburgh, PA 15219

Business Phone: (412) 235-5138

Business Fax: (412) 235-5110

E-Mail Address: wagnerwr@upmc.edu

EDUCATION and TRAINING

UNDERGRADUATE:

1982-1986	The Johns Hopkins University Baltimore, Maryland	B.S. (with honors) Chemical Engineering

GRADUATE:

1986-1991	The University of Texas at Austin Austin, TX	Ph.D. Chemical Engineering

---

APPOINTMENTS and POSITIONS

ACADEMIC:

7/01-	McGowan Institute for Regenerative Medicine University of Pittsburgh	Deputy Director

	Pittsburgh, PA	
12/06 -	Department of Surgery University of Pittsburgh Pittsburgh, PA	Professor of Surgery (with tenure)
12/06 -	Department of Chemical Engineering University of Pittsburgh	Professor of Chemical Engineering
12/06 -	Department of Bioengineering University of Pittsburgh	Professor of Bioengineering
7/99 – 12/06	Department of Surgery University of Pittsburgh Pittsburgh, PA	Associate Professor of Surgery (with tenure)
7/99 - 12/06	Department of Chemical Engineering University of Pittsburgh	Associate Professor of Chemical Engineering
7/99 - 12/06	Department of Bioengineering University of Pittsburgh	Associate Professor of Bioengineering
9/91 - 6/99	Department of Surgery University of Pittsburgh	Assistant Professor of Surgery
9/91- 6/99	Department of Chemical Engineering University of Pittsburgh	Assistant Professor of Chemical Engineering
9/96 – 6/99	Department/Program of Bioengineering University of Pittsburgh	Core Faculty
9/86 – 3/91	Department of Chemical Engineering The University of Texas at Austin Austin, TX	Research Associate

NON-ACADEMIC:

1985-1986	Engineering Materials Division City of Phoenix Phoenix, AZ	Research Assistant

---

MEMBERSHIPS in PROFESSIONAL and SCIENTIFIC SOCIETIES

1986 American Institute of Chemical Engineers

1986	Tau Beta Pi Engineering Honor Society
1987	Phi Kappa Phi Honor Society
1992	Fellow, Council on Arteriosclerosis, Thrombosis and Vascular Biology, American Heart Association
1992	American Society for Artificial Internal Organs
1992	Society for Biomaterials
1993	American Chemical Society
2000	Biomedical Engineering Society
2000	Fellow, American Institute for Medical and Biological Engineering
2001	Tissue Engineering Society – International
2005	Tissue Engineering and Regenerative Medicine International Society

---

HONORS

1986	Tau Beta Pi Engineering Honor Society, The Johns Hopkins University
1986	Graduating General and Departmental Honors, The Johns Hopkins University
1987	Phi Kappa Phi Honor Society, The University of Texas at Austin
1989-1990	Engineering Foundation Endowed Presidential Scholarship, University of Texas
1989-1990	Shell Foundation Fellowship, University of Texas
1992	Fellowship Travel Award, American Society for Artificial Internal Organs
1996	Tissue Engineering Society Travel Award – Pittsburgh Tissue Engineering Initiative
1997	Selected Excellence Paper – Society for Biomaterials Annual Meeting
2000	Elected to the College of Fellows – American Institute for Medical and Biological Engineering (AIMBE)
2000	Biomedical Engineering Society Undergraduate Research and Design Award (Advisor)
2001	ASAIO Biomedical Engineering Student Fellowship Award (Advisor)
2001	Fellow, American Heart Association and the Council on Arteriosclerosis, Thrombosis, and Vascular Biology
2001	First place at American Institute for Chemical Engineers National Student Poster Paper Competition (Advisor)
2002	First place, ASAIO Paul Malchesky Student Abstract Fellowship (Advisor)
2003	First place, American Heart Association Fellows' Research Day (Advisor)

2003	Chairman, Gordon Conference on Biomaterials: Biocompatibility and Tissue Engineering (Vice-Chairman in 2001)
2004	Selected as Founding Editor, *Acta Biomaterialia*
2004	Deutsche Forschungsgemeinschaft (DFG), Review Panel for Establishment of a National Research Center in Regenerative Medicine
2005	Author of a Top 5 "Hot Talks/Cool Papers" of 2005 Materials Research Society Fall Meeting
2006	Selected as one of the "*Scientific American 50*", the magazine's annual list recognizing leaders in science and technology from the research, business and policy fields.

PUBLICATIONS

Refereed Articles:

1. **Wagner WR**, Hubbell JA: Local thrombin synthesis and fibrin formation in an in vitro thrombosis model result in platelet recruitment and thrombus stabilization on collagen in heparinized blood. *J Lab Clin Med* 116:636-650 (1990).

2. Hubbell JA, Pohl PI, **Wagner WR**: The use of laser-light scattering and controlled shear in platelet aggregometry. *Thromb Haemost* 65:601-607 (1991).

3. **Wagner WR**, Hubbell JA: ADP receptor antagonists and converting enzyme systems reduce platelet deposition onto collagen. *Thromb Haemost* 67:461-467 (1992).

4. **Wagner WR**, Hubbell JA: Evidence for a role in thrombus stabilization for thromboxane A_2 in human platelet deposition on collagen. *J Lab Clin Med* 119:690-697 (1992).

5. **Wagner WR**, Johnson PC, Kormos RL, Griffith BP: Evaluation of bioprosthetic valve-associated thrombus in ventricular assist device patients. *Circulation* 88:2023-2029 (1993).

6. **Wagner WR**, Johnson PC, Thompson KA, Marrone GC: Heparin-coated cardiopulmonary bypass circuits: hemostatic alterations and postoperative blood loss. *Ann Thorac Surg* 58:734-741 (1994).

7. Andreopoulos FM, Deible CR, Stauffer MT, Weber S, **Wagner WR**, Beckman EJ, Russell AJ: Photoreversible hydrogel synthesis via photopolymerization of PEG-based polymers. *J Am Chem Soc* 118:6235-6240 (1996).

8. **Wagner WR**, Pachence JM, Ristich J, Johnson PC: Comparative in vitro analysis of topical hemostatic agents. *J Surg Res* 66:100-108 (1996).

9. Laghrissi-Thode F, **Wagner WR**, Pollock BG, Johnson PC, Finkel MS: Elevated platelet factor 4 and β-thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biol Psychiatry* 42:290-295 (1997).

10. Villanueva FS, Jankowski RJ, Manaugh C, **Wagner WR**: Albumin microbubble adherence to human coronary endothelium: implications for assessment of endothelial function using myocardial contrast echocardiography. *J Am Coll Cardiol* 30:689-693 (1997).

11. **Wagner WR**, Muzzio D, Rilo HR, Deglau T, Ataai MM, Michalopolous G, Block GD: Effect of growth factors and defined medium on primary hepatocyte culture on polyester carriers with varying surface treatment. *Tissue Eng* 3:289-301 (1997).

12. Jankowski RJ, Severyn DA, Vorp DA, **Wagner WR**: The effect of retroviral transduction on human endothelial cell phenotype and adhesion to Dacron vascular grafts. *J Vasc Surg* 26:676-684 (1997).

13. Deible CR, Beckman EJ, Russell AJ, **Wagner WR**: Creating molecular barriers to acute platelet deposition on damaged arteries with reactive polyethylene glycol. *J Biomed Mater Res* 41:251-256 (1998).

14. Wilhelm CR, Ristich J, Kormos RL, **Wagner WR**: Monocyte tissue factor expression and ongoing complement generation in ventricular assist device patients. *Ann Thorac Surg* 65:1071-1076 (1998).

15. Baker LC, Davis WC, Autieri J, Watach M, Yamazaki K, Litwak P, **Wagner WR**: Flow cytometric assays to detect platelet activation and aggregation in device-implanted calves. *J Biomed Mater Res* 41:312-321 (1998).

16. Villanueva FS, Jankowski RJ, Klibanov S, Pina ML, Alber S, Watkins SC, **Wagner WR**: Microbubbles targeted to intercellular adhesion molecule-1 bind to activated coronary artery endothelial cells. *Circulation* 98:1-5 (1998).

17. Baker LC, Kameneva MV, Watach MJ, Litwak P, **Wagner WR**: Assessment of bovine platelet life span with biotinylation and flow cytometry. *Artif Organs* 22:799-803 (1998).

18. Deible CR, Petrosko P, Johnson PC, Beckman EJ, Russell AJ, **Wagner WR**: Molecular barriers to biomaterial thrombosis by modification of surface proteins with polyethylene glycol. *Biomaterials* 19:1885-1893 (1998).

19. Sorensen EN, Burgreen GW, **Wagner WR**, Antaki JF: Computational simulation of platelet deposition and activation: I. Model development and properties. *Ann Biomed Eng* 27:436-448 (1999).

20. Sorensen EN, Burgreen GW, **Wagner WR**, Antaki JF: Computational simulation of platelet deposition and activation: II. Results for Poiseuille flow over collagen. *Ann Biomed Eng* 27:449-458 (1999).

21. Orban JM, Chapman TM, **Wagner WR**, Jankowski R: Easily grafted polyurethanes with reactive main chain functional groups. Synthesis, characterization, and antithrombogenicity of poly(ethylene glycol)-grafted poly(urethanes). *Journal of Polymer Science: Part A: Polymer Chemistry* 37:3441-3448 (1999).

22. Klibanov AL, Hughes MS, Villanueva FS, Jankowski RJ, **Wagner WR**, Wojdyla JK, Wible JH, Brandenburger GH: Targeting and ultrasound imaging of microbubble-based contrast agents. *Magnetic Resonance Materials in Physics, Biology and Medicine (MAGMA)* 8:177-184 (1999).

23. Wilhelm CR, Ristich J, Knepper LE, Holubkov R, Wisniewski SR, Kormos RL, **Wagner WR**: Measurement of hemostatic indices in conjunction with transcranial doppler sonography in ventricular assist device patients. *Stroke* 30:2554-2561 (1999).

24. Schaub RD, Kameneva MV, Borovetz HS, **Wagner WR**: Assessing acute platelet adhesion on opaque metallic and polymeric biomaterials with fiber optic microscopy. *J Biomed Mater Res* 49:460-468 (2000).

25. Gartner MJ, Wilhelm CR, Gage KL, Pham SM, Fabrizio C, **Wagner WR**: Modeling flow effects on thrombotic deposition in a membrane oxygenator. *Artif Organs* 24:29-36 (2000).

26. Laghrissi-Thode F, Pollock BG, **Wagner WR**: Evaluation of platelet activation in depressed patients with ischemic heart disease after paroxetine or nortriptyline treatment. *J Clin Psychopharmacol* 20:137-140 (2000).

27. Heesch CM, Wilhelm CR, Ristich J, Adnane J, Bontempo FA, **Wagner WR**: Cocaine activates platelets and increases the formation of circulating platelet containing microaggregates in humans. *Heart* 83:688-695 (2000).

28. Panza JL, **Wagner WR**, Rilo HLR, Rao RH, Beckman EJ, Russell AJ. Treatment of rat pancreatic islets with reactive PEG. *Biomaterials* 21:1155-1164 (2000).

29. **Wagner WR**, Schaub RD, Sorensen EN, Snyder TA, Wilhelm CR, Winowich S, Borovetz HS, Kormos RL: Blood biocompatibility analysis in the setting of ventricular assist devices. *J Biomater Sci Polym Ed* 11:1239-1259 (2000).

30. Whyte EM, Pollock BG, **Wagner WR**, Mulsant BH, Ferrell RE, Mazumdar S, Reynolds CFIII: Influence of serotonin-transporter-linked promoter region polymorphism on platelet activation in geriatric depression. *Am J Psychiatry* 158:2074-2076 (2001).

31. Burchenal JEB, Deible CR, Deglau TE, Russell AJ, Beckman EJ, **Wagner WR**: Polyethylene glycol diisocyanate decreases platelet deposition after balloon injury of rabbit femoral arteries. *J Thromb Thrombolysis* 13:27-33 (2002).

32. Guan J, Sacks MS, Beckman EJ, **Wagner WR**: Synthesis, characterization and cytocompatibility of elastomeric, biodegradable poly(ester-urethane)ureas based on poly(caprolactone) and putrescine. *J Biomed Mater Res* 61:493-503 (2002).

33. Snyder TA, Watach MJ, Litwak KN, **Wagner WR**: Platelet activation, aggregation, and life span in calves implanted with axial flow ventricular assist devices. *Ann Thorac Surg* 73:1933-1938 (2002).

34. Gage KL, Gartner MJ, Burgreen GW, **Wagner WR**: Predicting membrane oxygenator pressure drop using computational fluid dynamics. *Artif Organs* 26:600-607 (2002).

35. Weller GER, Villanueva FS, Klibanov AL, **Wagner WR**: Modulating targeted adhesion of an ultrasound contrast agent to dysfunctional endothelium. *Ann Biomed Eng* 30:1012–1019 (2002).

36. Lu E, **Wagner WR**, Schellenberger U, Abraham JA, Klibanov AL, Woulfe SR, Csikari MM, Fischer D, Schreiner GF, Brandenburger GH, Villanueva FS: Targeted in vivo labeling of receptors for vascular endothelial growth factor: Approach to identification of ischemic tissue. *Circulation* 108:97-103 (2003).

37. Eash HJ, Frankowski BJ, Litwak K, **Wagner WR**, Hattler BG, Federspiel WJ: Acute in-vivo testing of a respiratory assist catheter: Implants in calves versus sheep. *ASAIO J* 49:370-377 (2003).

38. Weller GER, Lu E, Csikari MM, Klibanov AL, Fischer D, **Wagner WR**, Villanueva FS: Ultrasound imaging of acute cardiac transplant rejection with microbubbles targeted to intercellular adhesion molecule-1. *Circulation* 108:218-24 (2003).

39. Guan J, Sacks MS, Beckman EJ, **Wagner WR**: Biodegradable poly(ether ester urethane)urea elastomers based on poly(ether ester) triblock copolymers and putrescine: synthesis, characterization and cytocompatibility. *Biomaterials* 25:85-96 (2004).

40. Stankus JJ, Guan J, **Wagner WR**: Fabrication of biodegradable, elastomeric scaffolds with sub-micron morphologies. *J Biomed Mater Res* 70A:603-14 (2004).

41. Guan J, Fujimoto KL, Sacks MS, **Wagner WR**: Preparation and characterization of highly porous, biodegradable polyurethane scaffolds for soft tissue applications. *Biomaterials* 26:3961-71 (2005).

42. Weller GER, Wong MKK, Modzelewski RA, Lu E, Klibanov AL, **Wagner WR**, Villanueva FS: Ultrasonic imaging of tumor angiogenesis using contrast microbubbles targeted via the tumor-binding peptide arginine-arginine-leucine. *Cancer Res* 65:533-539 (2005).

43. Wu J, Antaki JF, Snyder TA, **Wagner WR**, Borovetz HS, Paden BE: Design optimization of blood shearing instrument by computational fluid dynamics. *Artif Organs* 29:482-489 (2005).

44. Guan J, **Wagner WR**: Synthesis, characterization and cytocompatibility of polyurethaneurea elastomers with designed elastase sensitivity. *Biomacromolecules* 6:2833-2842 (2005).

45. Wu J, Antaki JF, **Wagner WR**, Snyder TA, Paden BE, Borovetz HS: Elimination of adverse leakage flow in a miniature pediatric centrifugal blood pump by computational fluid dynamics-based design optimization. *ASAIO J* 51:636–643 (2005).

46. Weller GER, Villanueva FS, Tom E, **Wagner WR**: Targeted ultrasound contrast agents: In vitro assessment of endothelial dysfunction and multi-targeting to ICAM-1 and sialyl Lewis^x. *Biotechnol Bioeng* 92:780-788 (2005).

47. Stankus JJ, Guan J, Fujimoto K, **Wagner WR**: Microintegrating smooth muscle cells into a biodegradable, elastomeric fiber matrix. *Biomaterials* 27:735–744 (2006).

48. Xu H, Kaar JL, Russell AJ, **Wagner WR**: Characterizing the modification of surface proteins with poly(ethylene glycol) to interrupt platelet adhesion. *Biomaterials* 27:3125–3135 (2006).

49. Sacks MS, Courtney T, Stankus J, Guan J, **Wagner WR**: Analysis and design of tissue engineered scaffolds that mimic soft tissue mechanical anisotropy. *Biomaterials* 27:3631-3638 (2006).

50. Guan J, Stankus JJ, **Wagner WR**: Development of composite porous scaffolds based on collagen and biodegradable poly(ester urethane)urea. *Cell Transplant* 15(S1):17-27 (2006).

51. Snyder TA, Eash HJ, Litwak KN, Frankowski BJ, Hattler BG, Federspiel WJ, **Wagner WR**: Blood biocompatibility assessment of an intravenous gas exchange device. *Artif Organs* 30:657–664 (2006).

52. Soletti L, Nieponice A, Guan J, Stankus J, **Wagner WR**, Vorp DA: A seeding device for tissue engineered tubular structures. *Biomaterials* 27:4863-4870 (2006).

53. Snyder TA, Tsukui H, Kihara S, Akimoto T, Litwak KN, Kameneva MV, Yamazaki K, **Wagner WR**: Preclinical biocompatibility assessment of the EVAHEART ventricular

assist device: coating comparison and platelet activation. *J Biomed Mater Res A* (in press).

54. Fujimoto KL, Guan J, Oshima H, Sakai T, **Wagner WR**: In vivo evaluation of a porous, elastic, biodegradable patch for reconstructive cardiac procedures. *Ann Thorac Surg* (in press).

55. Snyder TA, Litwak KN, Tsukui H, Akimoto T, Kihara S, Yamazaki K, **Wagner WR**: Leukocyte-platelet aggregates and monocyte tissue factor expression in bovines implanted with ventricular assist devices. *Artif Organs* (in press).

56. Deglau TE, Johnson JD, Villanueva FS, **Wagner WR**: Targeting microspheres and cells to PEG-modified biological surfaces. *J Biomed Mater Res A* (in press).

57. Villanueva FS, Lu E, Bowry S, Kilic S, Tom E, Wang J, Gretton J, Pacella JJ, **Wagner WR**: Myocardial Ischemic Memory Imaging Using Molecular Echocardiography. *Circulation* (in press).

Review Articles & Book Chapters:

58. Eidelman BH, Obrist WD, **Wagner WR**, Kormos R, Griffith B: Cerebrovascular complications associated with the use of artificial circulatory support services. *Neurol Clin* 11:463-474, (1993).

59. **Wagner WR**, Johnson PC: Therapeutic techniques for reducing thrombosis following cardiovascular implants. *Probl Gen Surg* 11:241-264, (1994).

60. Yamazaki K, Kameneva M, **Wagner W**, Antaki J, Tatka J, Kerrigan J, Tomczak J, Yang Z, Konishi H, Borovetz H, Griffith B, Koyanagi H, Kormos R: Bearing seizure in a rotational blood pump: mechanism and potential solutions. Artificial Heart 5: Heart Replacement, Springer-Verlag, New York, 371-376 (1996).

61. Jankowski RJ, **Wagner WR**: Directions in cardiovascular tissue engineering. *Clin Plast Surg* 26:605-616, (1999).

62. **Wagner WR**, Gage KL: Thrombosis and thromboembolism in stent grafts: evaluating Virchow's triad. Stent Graft Update, Medical and Engineering Publishers, Washington, DC, 125-140, (2000).

63. Villanueva FS, **Wagner WR**, Klibanov, AL: Targeted ultrasound contrast agents: identification of endothelial dysfunction. Ultrasound Contrast Agents: Basic Principles and Clinical Applications, 2nd Edition, Martin Dunitz Publishers, London, 353-365, (2001).

64. Villanueva FS, Klibanov A, **Wagner WR**: Microbubble-endothelial cell interactions as a basis for assessing endothelial function. *Echocardiography*. 19:427-438 (2002).

65. Gage KL, **Wagner WR**: Cardiovascular Devices. Standard Handbook of Biomedical Engineering and Design, McGraw-Hill, New York 20.1-20.48, (2003).

66. **Wagner WR**, Borovetz HS, Griffith BP: Implantable cardiac assist devices. Biomaterials Science: An Introduction to Materials in Medicine, 2nd Edition, Academic Press, San Diego, CA, (2004).

67. Villanueva FS, **Wagner WR**, Vannan MA, Narula J. Targeted ultrasound imaging using microbubbles. *Cardiol Clin.* 22:283-98 (2004).

68. Stankus JJ, Guan J, **Wagner WR**. Elastomers, biodegradable. Encyclopedia of Biomaterials and Biomedical Engineering. G.E. Wnek and G.L. Bowlin, Eds., Marcel Dekker, N.Y., (2004).

69. Ramaswami P, **Wagner WR**. Cardiovascular tissue engineering. An Introduction to Biomaterials. S.A. Guelcher and J.O. Hollinger, Eds., CRC Press, Boca Raton, FL, (2006).

70. Wearden PD, Morell VO, Keller BB, Webber SA, Borovetz HS, Badylak SF, Boston JR, Kormos RL, Kameneva MV, Simaan M, Snyder TA, Tsukui H, **Wagner WR**, Antaki JF, Diao C, Vandenberghe S, Gardiner J, Li CM, Noh D, Paden D, Paden B, Wu J, Bearnson GB, Jacobs G, Kirk J, Khanwilkar P, Long JW, Miles S, Hawkins JA, Kouretas PC, Shaddy RE. The PediaFlow pediatric ventricular assist device. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu.* 9:92-98 (2006).

71. Borovetz HS, Badylak S, Boston JR, Johnson C, Kormos R, Kameneva MV, Simaan M, Snyder TA, Tsukui H, **Wagner WR**, Woolley J, Antaki J, Diao C, Vandenberghe S, Keller B, Morell V, Wearden P, Webber S, Gardiner J, Li CM, Paden D, Paden B, Snyder S, Wu J, Bearnson G, Hawkins JA, Jacobs G, Kirk J, Khanwilkar P, Kouretas PC, Long J, Shaddy RE. Towards the development of a pediatric ventricular assist device. *Cell Transplant.* 15(S1):69-74 (2006).

72. Guan J, Stankus JJ, **Wagner WR**. Soft tissue scaffolds. Encyclopedia of Biomedical Engineering. G. Pins, Ed., J. Wiley and Sons (2006).

Proceedings Manuscripts:

73. **Wagner WR**, Johnson PC, Heil BV, Thompson KA, Kormos RL, Griffith BP: Thrombin activity resides on LVAD Dacron inflow and outflow grafts. *ASAIO J* 38:M634-M637, (1992).

74. Schaub RD Jr., Borovetz HS, Morgan SJ, **Wagner WR**: A new fiber optic probe for cellular visualization. *ASAIO J* 41:M665-M669, (1995).

75. Konishi R, Shimizu R, Firestone L, Walters FR, **Wagner WR**, Federspiel WJ, Konishi H, Hattler BG: Nitric oxide prevents human platelet adhesion to fiber membranes in whole blood. *ASAIO J* 42:M850-M853, (1996).

76. Thomas DC, Butler KC, Taylor LP, LeBlanc P, Griffith BP, Kormos RL, Borovetz HS, Litwak P, Kameneva MV, Choi S, Burgreen GW, **Wagner WR**, Wu Z, Antaki JF: Continued development of the Nimbus/University of Pittsburgh (UOP) axial flow left ventricular assist system. *ASAIO J* 43:M564-M566, (1997).

77. Deible CR, Burchenal JEB, Beckman EJ, Russell AJ, **Wagner WR**: Covalently attached polyethylene glycol reduces platelet deposition in vivo. *Proceedings of the Topical Conference on Biomaterials, Carriers for Drug Delivery, and Scaffolds for Tissue Engineering* pp. 49-51 (1997).

78. Panza JL, Rilo HR, Rao HR, Lakey JRT, **Wagner WR**, Beckman EJ, Russell AJ: Strategies for covalent modification of pancreatic islet capsules with polymers for possible immunoisolation. *Proceedings of the Topical Conference on Biomaterials, Carriers for Drug Delivery, and Scaffolds for Tissue Engineering* pp. 244-246 (1997).

Abstracts:

1. **Wagner WR**, Hubbell JA, McIntire LV, Mann KG: Importance of thrombin synthesis in mural thrombosis on collagen-coated glass. *Circulation Suppl* 78:II-312 (1988).

2. **Wagner WR**, Hubbell JA: The importance of thrombin synthesis and fibrin formation in platelet recruitment and thrombus stabilization on model subendothelia. *Thromb Haemostas* 62:131 (1989).

3. **Wagner WR**, Hubbell JA: The role of ADP in mural thrombosis and the effect of ATP at low concentrations. *Theodore S. Zimmerman Memorial Conference: Progress in Vascular Biology, Hemostasis and Thrombosis Abstracts* (1990).

4. **Wagner WR**, Hubbell JA: The role of ADP in platelet deposition on collagen under defined shear: inhibition by ADP receptor antagonists and converting enzyme systems, and an effect on cAMP. *Thromb Haemostas* 65:1113 (1991).

5. **Wagner WR**, Hubbell JA: Thromboxane A_2 supports human platelet deposition on collagen: a role in thrombus stabilization in addition to platelet recruitment. *Thromb Haemostas* 65:1113 (1991).

6. Johnson PC, **Wagner WR**, Garrett KO, Pristas JM, Kormos RL, Griffith BP: Hematologic changes associated with a cardiac assist device. *Blood* 78:215a (1991).

7. Johnson PC, Heil B, **Wagner WR**: LVAD thrombogenicity: role of Dacron inflow and outflow grafts. *Proceedings of the Cardiovascular Science and Technology Conference*, Washington, p.128 (1991).

8. **Wagner WR**, Johnson PC, Winowich S, Pristas J: Evaluation of LVAD inflow and outflow valves and comparison between thromboembolic event and non-event patient groups. *Proceedings of the Cardiovascular Science and Technology Conference*, Washington, p.127 (1991).

9. **Wagner W**, Johnson P, Heil B, Thompson K, Kormos R, Griffith B: Thrombin activity resides on explanted LVAD Dacron inflow and outflow conduit. *ASAIO Abstracts*, p53 (1992).

10. **Wagner WR**, Johnson PC, Thompson K, Marrone GC: Thrombin generation occurs preferentially at the time of cardiothoracic tissue reperfusion in cardiopulmonary bypass for coronary artery bypass grafting. *Proceedings of the Cardiovascular Science and Technology Conference*, Washington, p.104 (1992).

11. **Wagner WR**, Johnson PC, Thompson KA, Kormos RL, Griffith BP: Thrombin and plasmin activity reside on Dacron conduits of ventricular assist device. Patients have elevated indicators of thrombin and plasmin activity. *Thromb Haemostas* 69:777 (1993).

12. **Wagner WR**, Johnson PC, Kormos RL, Griffith BP: The relationship of flow, platelet activation, and valvular thrombotic deposition to thromboembolism in ventricular assist device patients. *Thromb Haemostas* 69:996 (1993).

13. **Wagner WR**, Schaub RD, Shaffer F, Johnson PC, Kormos RL, Woodard J, Borovetz HS: Flow dynamics and thrombotic deposition within a ventricular assist device. *Extended Abstracts AIChE 1993 Annual Meeting* p.251 (1993).

14. **Wagner WR**, Marrone GC, Thompson KA, Johnson PC: Fibrinolysis and thrombin generation occur at the time of pulmonary reperfusion in cardiopulmonary bypass. *Transactions of the Society for Biomaterials* 16:140 (1993).

15. **Wagner WR**, Wilhelm CR, Thompson KA, Kormos RL, Griffith BP, Johnson PC: Thrombogenic indices in ventricular assist device patients: ongoing fibrin turnover and periodic platelet activation. *Proceedings of the Cardiovascular Science and Technology Conference*, Washington, p.217 (1993).

16. **Wagner W**, Wilhelm C, Gartner M, Fabrizio C, Pham S: Thrombus deposition and flow modeling in extracorporeal membrane oxygenation circuits. *ASAIO Abstracts*, p.57 (1994).

17. **Wagner WR**, Tiffany H, Thompson KA, Schultz JS, Johnson PC: Surface thrombin found on preclotted Dacron grafts mediates platelet deposition in vitro. *Transactions of the Society for Biomaterials* 17:3 (1994).

18. **Wagner WR**, Gartner MJ, Wilhelm CR: Computational fluid dynamics and quantitative image analysis applied to thrombotic deposition in a membrane oxygenator. *Annals of Biomedical Engineering* 22(s.1):17 (1994).

19. **Wagner WR**, Gartner MJ, Wilhelm CR: Predicting clinical thrombotic deposition in membrane oxygenators with computational fluid dynamics. *Proceedings of the Cardiovascular Science and Technology Conference*, Washington, p.116 (1994).

20. **Wagner WR**, Gartner MJ, Wilhelm CR, Pham SM, Fabrizio C: Applying computational fluid dynamics and quantitative assessment of clinical thrombotic deposition to a membrane oxygenator. *Extended Abstracts AIChE 1994 Annual Meeting* p.123 (1994).

21. Wilhelm C, Houston A, Griffith B, Kormos R, Johnson P, **Wagner W**: Platelet-leukocyte aggregates increase prior to neurologic events in ventricular assist device (VAD) patients. *ASAIO J* 41(supp):47 (1995).

22. Schaub R, Chen W, Deible C, Shaffer, Borovetz H, Griffith B, **Wagner W**: Visualizing blood cells with a new fiber optic probe. *ASAIO J* 41(supp):24 (1995).

23. Yamazaki K, Kameneva M, **Wagner W**, Antaki J, Tatka J, Kerrigan J, Litwak P, Konishi H, Macha M, Yang Z, Borovetz H, Griffith B, Kormos R: Bearing seizure in a rotational blood pump: mechanism and potential solutions. *ASAIO J* 41(supp):46 (1995).

24. Rilo HLR, Diaf A, Beckman EJ, Deible C, Russell AJ, Byrne ME, Rao AS, **Wagner WR**: Microencapsulation of isolated pancreatic islets with photocrosslinkable polyethylene glycol-based polymers. *Proceedings of Fifth IPITA Congress* (1995).

25. Wilhelm CR, Houston A, Kormos RL, Johnson PC, **Wagner WR**: Flow cytometric evaluation of circulating cellular aggregates in ventricular assist device patients. *Transactions of the Society for Biomaterials* 18:11 (1995).

26. Schaub RD, Chen W, Morgan S, Borovetz HS, **Wagner WR**: A novel fiber optic probe for blood cell visualization. *Extended Abstracts AIChE 1995 Annual Meeting*. (1995).

27. Muzzio D, Rilo HR, Ataai M, Block G, Michalopoulos G, **Wagner WR**: Hepatocyte culture on porous polystyrene carriers: response to substrate, media, and shear environment. *Extended Abstracts AIChE 1995 Annual Meeting*. (1995).

28. Knepper LE, Eidelman BH, **Wagner WR**: Transcranial Doppler detection of emboli in patients with left-ventricular assist devices (LVAD). *Stroke* 27:77 (1996).

29. Konishi R, Firestone L, **Wagner W**, Federspiel WJ, Konishi H, Shimizu R, Hattler B: Nitric oxide prevents human platelet adhesion on fiber membrane in whole blood. *ASAIO J* 42:72 (1996).

30. Andreopoulos F, Deible C, **Wagner W**, Weber S, Beckman E, Russell A: Synthesis and blood biocompatibility of photopolymerizable, branched PEG hydrogel. *ASAIO J* 42:16 (1996).

31. Deible CR, Chen CT, Beckman EJ, Russell AJ, **Wagner WR**: Covalently attached polyethylene glycol reduces platelet deposition onto damaged placental arteries. *Transactions of the 5th World Biomaterials Congress* 2:104 (1996).

32. Pachence JM, Ristich J, Johnson PC, **Wagner WR**: Comparative in vitro analysis of topical hemostatic biomaterials. *Transactions of the 5th World Biomaterials Congress* 1:650 (1996).

33. Jankowski RJ, **Wagner WR**, Alibali P, Ghandi R, Villanueva FS: Albumin microbubbles preferentially adhere to the extracellular matrix of inflamed human coronary endothelium. *J Am Coll Cardiol* 27:298A (1996).

34. Deible CR, Beckman EJ, Russell AJ, **Wagner WR**: Reducing platelet deposition onto damaged arteries with covalently attached polyethylene glycol. *AIChE Annual Meeting Abstracts* (1996).

35. Schaub RD Jr., Shaffer FD, Borovetz HS, **Wagner WR**: Measuring temporal platelet deposition on opaque surfaces. *AIChE Annual Meeting Abstracts* (1996).

36. Jankowski RJ, **Wagner WR**, Manaugh CA, Villanueva FS: Interaction of albumin microbubbles with endothelial cells and their matrix. *AIChE Annual Meeting Abstracts* (1996).

37. Deible CR, Russell AJ, Beckman EJ, **Wagner WR**: Covalently attached polyethylene glycol reduces platelet deposition onto damaged placental arteries. *Circulation* 94:I-615 (1996).

38. Wilhelm CR, Ristich J, Houston A, Kormos RL, **Wagner WR**: Ongoing complement and monocyte activation in ventricular assist device patients. *Circulation* 94:I-293 (1996).

39. Jankowski RJ, **Wagner WR**, Manaugh CA, Villanueva FS: Albumin microbubbles preferentially adhere to inflamed cultured coronary artery endothelial cells perfused with cardioplegia. *Circulation* 94:I-574 (1996).

40. Deible CR, Beckman EJ, Russell AJ, **Wagner WR**: Covalent modification of damaged arterial tissue to reduce thrombosis. *Inaugural Meeting of the Tissue Engineering Society Abstracts* p.52 (1996).

41. Deible CR, Petrosko P, Johnson PC, Beckman EJ, Russell AJ, **Wagner WR**: Reducing thrombosis in synthetic microconduits by modifying surface proteins. *Inaugural Meeting of the Tissue Engineering Society Abstracts* p. 38 (1996).

42. Jankowski RJ, Connor IP, Vorp DA, **Wagner WR**: The effect of retroviral transduction on human endothelial cell phenotype. *Inaugural Meeting of the Tissue Engineering Society Abstracts* p.51 (1996).

43. Schaub RD Jr., Shaffer FD, Borovetz HS, **Wagner WR**: Assessing blood compatibility of opaque biomaterials with remote fiber optic microscopy. *Transactions of the Society for Biomaterials* 20:17 (1997).

44. Jankowski RJ, Severyn DA, Vorp DA, **Wagner WR**: Retroviral transduction does not adversely alter human endothelial cell phenotype on Dacron vascular grafts. *Transactions of the Society for Biomaterials* 20:84 (1997).

45. Deible CR, Markowitz PF, Petrosko P, Johnson PC, Beckman EJ, Russell AJ, **Wagner WR**: Covalently attached polyethylene glycol reduces platelet deposition onto protein adsorbed biomaterials. *Transactions of the Society for Biomaterials* 20:109 (1997).

46. Wilhelm CR, Ristich J, Kormos RL, **Wagner WR**: Evidence of complement mediated platelet-leukocyte aggregation and monocyte tissue factor expression in ventricular assist device patients. *Transactions of the Society for Biomaterials* 20:272 (1997).

47. Ristich J, Sierra DH, **Wagner WR**: Evaluation of platelet activation and deposition onto collagen and fibrin-based hemostatic agents. *Transactions of the Society for Biomaterials* 20:328 (1997).

48. Villanueva FS, Jankowski R, Ahsai D, Krishnan A, Muddasani S, Pina M, **Wagner WR**: Cold temperature augments albumin microbubble adherence to cardioplegia perfused human coronary endothelial cells. *J Am Coll Cardiol* 29:301A (1997).

49. Villanueva FS, Jankowski R, Klibanov S, Pina ML, Mudassani S, Mills JD, **Wagner WR**: Microbubbles targeted to intercellular adhesion molecule-1 bind to activated coronary artery endothelial cells: a novel approach to assessing endothelial function using myocardial contrast echocardiography. *Circulation* 96:I-457 (1997).

50. Burchenal J, Deible CR, Beckman EJ, Russell AJ, **Wagner WR**: Covalently-attached polyethylene glycol reduces platelet deposition after vascular injury in vivo. *Circulation* 96:I-722 (1997)

51. Powell C, Hebda P, Beckman E, Russell A, **Wagner W**: Covalent coupling of epidermal growth factor and gly-arg-gly-asp to surfaces to promote cell adhesion. *ASAIO J* 43:1 (1997).

52. Gartner M, Wilhelm C, **Wagner W**: Computational fluid dynamics applied to membrane oxygenator design and optimization. *ASAIO J* 43:14 (1997).

53. Baker L, Davis W, Autier J, Watach M, Yamazaki K, Litwak P, **Wagner W**: Flow cytometric assays developed to detect platelet activation and aggregation in device-implanted calves. *ASAIO J* 43:45 (1997).

54. Deible CR, Burchenal J, Beckman EJ, Russell AJ, **Wagner WR**: Covalently attached polyethylene glycol reduces platelet deposition in vivo. *AIChE Annual Meeting Abstracts* Abstract 43a (1997).

55. Wilhelm CR, Ristich J, Kormos RL, **Wagner WR**: Potential links between inflammation and thrombosis in ventricular assist device patients. *Thromb Haemostas* Supplement:104 (1997).

56. Schaub RD, Borovetz HS, **Wagner WR**: Real-time assessment of temporal platelet deposition on an interior surface of a centrifugal blood pump. *ASAIO J* 44:12 (1998).

57. Jankowski R, **Wagner W**, Klibanov S, Pina M, Alber S, Watkins S, Villanueva F: Targeted ultrasound microbubble contrast agents may be used to assess endothelial cell phenotype. *ASAIO J* 44:96 (1998).

58. Basalyga DM, **Wagner WR**, Beer-Stolz D, Fenyus ML, Villanueva FS: Albumin microbubbles adhere to exposed extracellular matrix of perfused whole vessels. *Circulation* 98:I-290 (1998).

59. Baker LC, Davis WC, Watach M, Yamazaki K, Litwak P, **Wagner WR**: Measurement of platelet life span, circulating activated platelets and microaggregates in calves with cardiovascular devices using new flow cytometric techniques. *Transactions of the Society for Biomaterials* 21:54 (1998).

60. Wilhelm CR, Knepper LE, Ristich J, Kormos RL, **Wagner WR**: Hemostatic alterations, stroke, and the detection of formed element emboli with transcranial doppler ultrasound in ventricular assist device patients. *Transactions of the Society for Biomaterials* 21:55 (1998).

61. Deible CR, Burchenal JEB, Russell AJ, Beckman EJ, **Wagner WR**: Tissue-reactive polyethylene glycol reduces platelet deposition after balloon injury in rabbit femoral arteries. *Transactions of the Society for Biomaterials* 21:138 (1998).

62. Schaub RD, Borovetz HS, **Wagner WR**: On-line measurement of temporal platelet deposition on an interior surface of a centrifugal blood pump. *Transactions of the Society for Biomaterials* 21:302 (1998).

63. Gartner MJ, Federspiel WJ, Gage KL, **Wagner WR**: Predicting blood flow and oxygenation in membrane oxygenators using computational fluid dynamics. *AIChE Annual Meeting Abstracts* (1998).

64. Klibanov SL, Jankowski RJ, Mills JD, Mudassani S, Pina ML, Villanueva FS, **Wagner WR**: Developing targeted ultrasound microbubble contrast agents to assess vascular health. *AIChE Annual Meeting Abstracts* Abstract 280a (1998).

65. Clay C, **Wagner W**, Golec B, Podell S, Fenyus M, Weller G, Lohrmann R, Villanueva F: New insights into mechanisms of albumin microbubble adhesion to coronary endothelium using chemically modified microbubbles. *J Am Coll Cardiol* 33:407A (1999).

66. Snyder TA, Watach MJ, Litwak KN, Gordon LM, **Wagner WR**: Assessing circulating activated platelets and platelet consumption in calves implanted with an axial flow ventricular assist device. *Transactions of the Society for Biomaterials* 22:100 (1999).

67. Sorensen EN, Burgreen GW, **Wagner WR**, Antaki JF: Computational simulation of platelet-mediated thrombogenesis on biomaterials. *Transactions of the Society for Biomaterials* 22:204 (1999).

68. **Wagner WR**: Utilizing literature review to reinforce principles in a Biomaterials & Biocompatibility course. *Transactions of the Society for Biomaterials* 22:383 (1999).

69. Snyder TA, Watach MJ, Litwak KN, Gordon LM, **Wagner WR**: Quantifying thrombosis in ventricular assist device implanted calves. *ASAIO J* 45:142 (1999).

70. Sorensen EN, Winowich S, Schaub RS, Kormos RL, Borovetz HS, **Wagner WR**: Predicting neurologic events in ventricular assist device patients. *ASAIO J* 45:152 (1999).

71. Thomas D, Butler K, Taylor L, leBlanc P, Rintoul T, Petersen T, Griffith B, Kormos R, Borovetz H, Litwak P, Litwak K, Kameneva M, Choi S, Burgreen G, Wu J, Antaki J, Watach M, **Wagner W**: The Nimbus-University of Pittsburgh (UOP) axial flow left ventricular assist system. *ASAIO J* 45:162 (1999).

72. Snyder TA, Litwak KN, Watach, MJ, **Wagner WR**: Shear activation of platelets in an axial flow ventricular assist device.*Annual International Conference of the IEEE Engineering in Medicine and Biology - Proceedings* 2:753 (1999).

73. Clay CA, Weller GER, Klibanov AL, Podell S, Greener Y, Jablonski EG, **Wagner WR**, Villanueva FS: Does fluorescent tagging of albumin microbubbles affect adhesion to endothelial cells? An in vitro study. *Circulation* 100(suppl.):2321 (1999).

74. Snyder TA, Litwak KN, Watach MJ, **Wagner WR**: Flow cytometric assays to quantify platelet activation, aggregation, and life span in ventricular assist device implanted calves. *Symposium Notebook: Surfaces in Biomaterials '99*, 161-163 (1999).

75. Snyder TA, Watach MJ, Litwak KN, Gordon LM, **Wagner WR**: Platelet activation associated with increased shear in calves implanted with axial flow ventricular assist devices. *Transactions of the Society for Biomaterials* 23:295 (2000).

76. Deglau TE, Litwak KN, Villanueva FS, **Wagner WR**: Surface modification of vascular tissue for targeted delivery of endothelial cells and microspheres. *AIChE Annual Meeting Abstracts* Abstract 286c (2000).

77. Xu H, Beckman EJ, Russell AJ, **Wagner WR**: Polymeric modification of surface proteins for reduced cell adhesion. *AIChE Annual Meeting Abstracts* Abstract 199a (2000).

78. Deglau TE, Litwak K, Villanueva FS, **Wagner WR**: Surface modification of vascular tissue for targeted delivery of endothelial cells and microspheres. *Annals of Biomedical Engineering*, 28:S23 (2000).

79. Villanueva FS, Lu EL, Csikari MM, Brown ML, Woulfe S, Fischer D, Abraham JA, Schreiner GD, Brandenburger GH, Klibanov AL, Schellenberger U, **Wagner WR:** Targeted in vivo scintigraphic imaging of receptors for vascular endothelial growth factor identifies ischemic tissue. *Circulation* 102 (suppl):1968 (2000).

80. Zenati MA, Nichols L, **Wagner WR**, Burckart GJ, Griffith BP: Robotic coronary artery bypass surgery on the beating heart. *Circulation* 102 (suppl):3560 (2000).

81. Deglau TE, Litwak KN, Villanueva FS, **Wagner WR**: Targeting microsphere delivery to labeled vascular tissue using biotin and neutravidin. *ASAIO J* 46:173 (2000).

82. Snyder TA, Watach MJ, Litwak KN, **Wagner WR**: Platelet activation following rotary pump speed increase. *ASAIO J* 46:174 (2000).

83. Xu H, Beckman EJ, Russell AJ, **Wagner WR**: Characterizing polymer modification of adsorbed proteins to reduce platelet deposition. *Transactions of the Society for Biomaterials* 24:274 (2001).

84. Deglau TE, Litwak KN, Villanueva FS, **Wagner WR**: Targeted delivery of microspheres and endothelial cells to damaged vascular tissue. *Transactions of the Society for Biomaterials* 24:291 (2001).

85. Snyder TA, Watach MA, Gordon LM, Litwak KN, Lund LW, Golob JF, Federspiel WJ, Hattler BG, **Wagner WR**: Evaluating biocompatibility in an intravenous membrane oxygenator. *Transactions of the Society for Biomaterials* 24:423 (2001).

86. Fill BJ, Golledge SL, **Wagner WR**: Surface modification of microporous fibers for endothelialized oxygenator membranes. *Transactions of the Society for Biomaterials* 24:423 (2001).

87. Gage KL, Kinahan PE, Gartner MJ, **Wagner WR**: Imaging of flow inside membrane oxygenators using fluoroscopy. *ASAIO J* 47:130 (2001).

88. Snyder TA, Wu J, Antaki JF, Burgreen GW, **Wagner WR**: In vitro investigation of shear-induced platelet activation in axial flow VADs. *ASAIO J* 47:137 (2001).

89. Fill BJ, Golledge SL, **Wagner WR**: Endothelialization of oxygenator membranes through glow discharge surface treatment. *ASAIO J* 47:128 (2001).

90. **Wagner WR**: Biocompatibility challenges in cardiovascular devices and the need for biological interfaces. *Ann Biomed Eng* 29:S1 (2001).

91. Weller GE, Klibanov AL, Villanueva FS, **Wagner WR**: Controlling ultrasound contrast microbubble targeting to dysfunctional endothelium. *Ann Biomed Eng* 29:S63 (2001).

92. Guan J, Sacks M, Beckman EJ, **Wagner WR**: Synthesis and characterization of highly elastomeric, bioerodible poly(ester urethane)ureas. *Ann Biomed Eng* 29:S1 (2001).

93. Weller G, Klibanov S, **Wagner WR**, Villanueva FS: Variable antibody density on contrast microbubbles modulates targeted adhesion to dysfunctional endothelium. *Circulation* 104 (Suppl II):II-352 (2001).

94. Snyder TA, Kihara S, Litwak KN, Yamazaki K, **Wagner WR**: Thrombosis assessment in calves implanted with a centrifugal ventricular assist device. *Transactions of the Society for Biomaterials* 25:8 (2002).

95. Guan J, Sacks MS, Beckman EJ, **Wagner WR**: Synthesis, characterization and cytocompatibility of biodegradable poly(ester urethane)ureas. *Transactions of the Society for Biomaterials* 25:69 (2002).

96. Snyder TA, Lund L, Russian H, Litwak KN, Hattler BG, Federspiel WJ, **Wagner WR**: Assessing and improving the biocompatibility of an intravascular oxygenator. *Transactions of the Society for Biomaterials* 25:37 (2002).

97. Guan J, Sacks MS, Beckman EJ, **Wagner WR**: Synthesis of biodegradable poly(ether ester urethane)ureas for cardiovascular applications. *Transactions of the Society for Biomaterials* 25:423 (2002).

98. Guan J, Payne TR, Huard J, **Wagner WR**: Modification of biodegradable polyurethane surfaces to support the growth of a skeletal muscle-derived stem cell. *Transactions of the Society for Biomaterials* 25:89 (2002).

99. **Wagner WR**: Biodegradable elastomers for use in soft tissue engineering. *Engineering Tissue Growth Conference Abstracts* (2002).

100. Lu E, Black M, Fischer D, **Wagner WR**, Villanueva FS. Myocardial contrast echocardiography can be used to detect acute heart transplant rejection. *J Am Coll Cardiol* 39:360A (2002).

101. Snyder TA, Russian H, Litwak KN, Hattler BG, Federspiel WJ, **Wagner WR**: Assessing thrombosis of an intravascular respriratory support catheter. *ASAIO J* 48:154 (2002).

102. Snyder TA, Kihara S, Litwak KN, Yamazaki K,**Wagner WR**: Measurement of thrombosis in calves implanted with a centrifugal ventricular assist device. *ASAIO J* 48:153 (2002).

103. Weller GER, Villanueva FS, Klibanov AL, **Wagner WR**. Shear modulates adhesion of ultrasound contrast microbubbles targeted to dysfunctional endothelium. *Proceedings of the Second Joint EMBS-BMES Conference* 2002, Abstract 4.3.10.3, p.212 (2002).

104. Guan J, Sacks MS, **Wagner WR**. Development of a highly porous, flexible and biodegradable poly(ester urethane)urea scaffold for tissue engineering. *Proceedings of the Second Joint EMBS-BMES Conference*, Abstract 4.3.2.6, p.196 (2002).

105. Weller GER, Villanueva FS, Wong MKK, Modzelewski RA, Klibanov AL, **Wagner WR**. Ultrasound contrast microbubbles targeted to tumor angiogenesis specifically bind tumor-derived endothelial cells. *Proceedings of the Second Joint EMBS-BMES Conference*, Abstract 4.3.10.2, pgs.211-212 (2002).

106. Sorensen EN, Burgreen GW, **Wagner WR**, Antaki JF. Simulation of platelet deposition in disturbed flow. *Proceedings of the Second Joint EMBS-BMES Conference*, Abstract 2.1.8.5, p.153 (2002).

107. Weller GER, Lu E, Csikari MM, Klibanov AL, Fischer DW, **Wagner WR**, Villanueva FS. Ultrasound contrast microbubbles targeted to ICAM-1 detect acute heart transplant rejection. *Circulation* 106(Suppl II):II-378 (2002).

108. Weller GER, Wong MKK, Modzelewski RA, Klibanov AL, **Wagner WR**, Villanueva FS. Angiogenesis-targeted ultrasound contrast microbubbles preferentially adhere to tumor derived endothelium. *Circulation* 106(Suppl II):II-378 (2002).

109. Guan J, Sacks MS, **Wagner WR**: Development of a flexible, biodegradable scaffold capable of growth factor release. *Transactions of the Society for Biomaterials* 26:573 (2003).

110. Snyder TA, Udowenko MA, Litwak KN, Kihara SI, **Wagner WR**: Assessing ventricular assist device associated leukocyte activation in a bovine model. *Transactions of the Society for Biomaterials* 26:17 (2003).

111. Guan J, Sacks MS, **Wagner WR**: Porous, biodegradable elastomers from poly(ether ester urethane)urea for soft tissue engineering. *Transactions of the Society for Biomaterials* 26:117 (2003).

112. Stankus JJ, Guan J, **Wagner WR**: Electrospinning of poly(ester urethane)urea and collagen to construct biodegradable, elastomeric scaffolds with nanoscale fibers. *Transactions of the Society for Biomaterials* 26:268 (2003).

113. **Wagner WR**: Processing of elastomeric scaffolds for cardiovascular tissue engineering. *The Engineering Tissue Growth International Conference & Exposition Abstracts* (2003).

114. Snyder TA, Litwak KN, Kihara S, **Wagner WR**: Leukocyte activation following bovine VAD implantation. *ASAIO J* 49:169 (2003).

115. Fujimoto KL, Guan J, Sakai T, Oshima H, **Wagner WR**: Development of a porous, elastic, biodegradable patch for reconstructive cardiac procedures. *ASAIO J* 49:210 (2003).

116. Polk AA, Federspiel WJ, **Wagner WR**: Modification of microporous hollow fibers to support endothelial cell adhesion. *ASAIO J* 49:217 (2003).

117. Gage KL, Kinahan PE, Boada FE, **Wagner WR**: Computational prediction and fluoroscopic imaging of oxygenator flow dynamics. *ASAIO J* 49:218 (2003).

118. Weller GER, **Wagner WR**, Klibanov AL, Villanueva FS: Ultrasound contrast microbubbles targeted to ICAM-1 can discern degree of endothelial inflammation. *J Am Soc Echo* 16:560 (2003).

119. Stankus JJ, Guan J, **Wagner WR**: Creating biodegradable, elastic matrices with bioactivity and nanoscale features. *Proceedings of the2003 Annual Fall Meeting, Biomedical Engineering Society*, Abstract 2.P1.3, p.19 (2003).

120. Guan J, Sacks MS, **Wagner WR**: A porous, flexible and biodegradable polyurethane/collagen composite for soft tissue engineering. *Proceedings of the2003 Annual Fall Meeting, Biomedical Engineering Society*, Abstract 2.P1.32, p.25 (2003).

121. Henchir KA, **Wagner WR**, Federspiel WJ: Microfabrication of biohybrid artificial lungs. *Proceedings of the2003 Annual Fall Meeting, Biomedical Engineering Society*, Abstract 12.P3.5, p.203 (2003).

122. Fujimoto KL, Guan J, Oshima H, Sakai T, **Wagner WR**: Reconstruction of the right ventricular outflow tract with a biodegradable, elastic patch. *Proceedings of the 2003 Annual Fall Meeting, Biomedical Engineering Society*, Abstract 6.P4.30, p.96 (2003).

123. Weller GE, Villanueva FS, Wong MK, Modzelewski RA, **Wagner WR**: Contrast-enhanced ultrasound technique for the targeted molecular imaging of tumors. *Proceedings of the 2003 Annual Fall Meeting, Biomedical Engineering Society*, Abstract 8.6.4, p.134 (2003).

124. Weller GE, Villanueva FS, Lui E, Klibanov AL, Fischer DW, Csikari MM, **Wagner WR**: Targeted molecular imaging of transplant rejection using contrast-enhanced ultrasound. *Proceedings of the 2003 Annual Fall Meeting, Biomedical Engineering Society*, Abstract 8.6.5, p.134 (2003).

125. Guan J, Stankus J, Fujimoto K, **Wagner WR**: Soft tissue engineering with biodegradable elastomers. *35th Central Regional Meeting of the American Chemical Society Abstracts*, Abstract 36 (2003).

126. Weller GER, Wong MK, Modzelewski RA, Lu E, Klibanov AL, **Wagner WR**, Villanueva FS. Tumor vasculature can be imaged with ultrasound contrast microbubbles targeted via tumor-binding peptides. *Circulation* 108:2348 (2003).

127. Weller GER, Tom EM, Felix MM, **Wagner WR**, Villanueva FS. Multi-targeting enhances adhesion of ultrasound contrast microbubbles to inflammatory endothelium. *Circulation* 108:2355 (2003).

128. Nieponice A, Soletti L, Guan J, Huard J, **Wagner WR**, Vorp DA: Reconstruction of the right ventricular outflow tract with a novel, biodegradable elastomeric scaffold. *8th Annual Hilton Head Workshop: Cardiovascular Engineering Abstracts* p.34 (2004).

129. Lu E, Tom EM, Felix MM, Gretton J, Varghese RP, **Wagner WR**, Villanueva FS: In vivo microbubble binding to inflammatory endothelium via selectin targeting by Sialyl Lewis X. *J Am Coll Cardiol* 43:8A (2004).

130. Deglau TE, Villanueva FS, **Wagner WR**: Targeted delivery of microspheres to vascular tissue. *Regenerate: Tissue Engineering the Human Body*, Abstract P021 (2004).

131. Fujimoto K, Guan J, Oshima H, Sakai T, **Wagner WR**: In vivo evaluation of a porous, elastic, biodegradable patch for reconstructive cardiac procedures. *Transactions of the 7th World Biomaterials Congress*, Abstract 507 (2004).

132. Stankus JJ, Guan J, **Wagner WR**: Fibrous, elastic scaffolds fabricated from biodegradable poly(ester urethane)urea and collagen. *Transactions of the 7th World Biomaterials Congress*, Abstract 870 (2004).

133. Wong MKK, Modzelewski RA, Weller G, Villanueva FS, Henry D, Kirk JS, Brown CK, **Wagner WR**: Ultrasound contrast visualization of tumor vasculature in vivo by targeted microbubbles. *J Clin Oncol* 22:243S, Abstract 3198 (2004).

134. Snyder TA, Kihara S, Tsukui H, **Wagner WR**: Effects of surface modifications on in vivo biocompatibility in rotary blood pumps. *ASAIO J* 50:134 (2004).

135. Snyder TA, Antaki JF, Bearnson G, Boston R, Chen C, Gandhi S, Hawkins J, Jacobs G, Kameneva MV, Keller B, Khawilkar P, Kormos RL, Li CM, Long J, Miles S, Paden B, Paden D, Shaddy R, Simaan M, **Wagner W**, Webber S, Wells J, Wu J, Yount L,

Borovetz HS: Development of ventricular assist devices for infants and small children. *ASAIO J* 50:135 (2004).

136. Stankus J, Guan J, **Wagner WR**: Fabrication of fibrous scaffolds of sub-micron scale from biodegradable poly(ester urethane) urea and type I collagen. *Midwestern Tissue Engineering Consortium Abstracts*, Abstract 5-1 (2004).

137. Deglau TE, Villanueva FS, **Wagner WR**: In vivo surface modification of vascular tissue for targeted microsphere delivery. *Proceedings of the 2004 Annual Fall Meeting of the Biomedical Engineering Society*, Abstract 1229 (2004).

138. Guan J, **Wagner WR**: Synthesis and processing of elastase-sensitive, biodegradable polyurethane elastomers. *Proceedings of the 2004 Annual Fall Meeting of the Biomedical Engineering Society*, Abstract 1292 (2004).

139. Modzelewski RA, Weller GER, Wong MKK, Brown CK, Lu E, Klibanov AL, **Wagner WR**, Villanueva FS. Targeted tumor imaging with ultrasound in tumor-bearing mice by means of a tumor endothelium-specific binding peptide conjugated to perfluorobutane microbubbles. *Proc Am Assoc Cancer Res* 45:937 (2004).

140. Guan J, Stankus JJ, **Wagner WR**: Development of porous, flexible and biodegradable poly(ester urethane)urea scaffolds with surface attached RGDS for soft tissue construct development. *Biomaterials in Regenerative Medicine: The Advent of Combination Products Transactions* (2004).

141. Stankus JJ, Guan J, **Wagner WR**: Fibrous elastomeric poly(ester urethane)urea scaffolds incorporating collagen. *Biomaterials in Regenerative Medicine: The Advent of Combination Products Transactions* (2004).

142. Kilic S, Lu E, Tom E, Gretton J, **Wagner WR**, Villanueva FS. Modifications of lipid microbubble shell composition affect intravascular kinetics. *J Am Coll Cardiol* 45:270A, (2005).

143. Guan J, **Wagner WR**: Development of biodegradable and flexible thermosensitive hydrogels for soft tissue engineering. *Society For Biomaterials 30th Annual Meeting Transactions* p.56 (2005).

144. Draghi L, Stankus JJ, **Wagner WR**: Development of elastic, small diameter porous conduits amenable for use as neural growth guides. *Society For Biomaterials 30th Annual Meeting Transactions*, p.675 (2005).

145. Nieponice A, Guan J, Soletti L, Huard J, **Wagner WR**, Vorp DA: Development of a tissue engineered vascular graft based on biodegradable elastomer and muscle derived stem cells. *Society For Biomaterials 30th Annual Meeting Transactions,* p.58 (2005).

146. Courtney TD, Sacks M, Stankus JJ, Guan J, **Wagner WR**: Structural and mechanical characterization of poly (ester urethane) urea elastomeric scaffolds for cardiovascular soft tissue engineering. *Society For Biomaterials 30th Annual Meeting Transactions,* p.54 (2005).

147. Stankus JJ, Guan J, Fujimoto K, **Wagner WR**: Microintegration of smooth muscle cells into a biodegradable elastomer. *Society For Biomaterials 30th Annual Meeting Transactions*, p.182 (2005).

148. Snyder TA, Kamenava MV, Monzyk BF, Burckle EC, Vollmer AP, Thorsen TA, Gilbert RJ, Dasse KA, Martin PM, Borovetz HS, **Wagner WR**: Preliminary hemocompatibility assessment of a photolytic artificial lung. *Society For Biomaterials 30th Annual Meeting Transactions*, p.290 (2005).

149. Sacks MS, Courtney T, Stankus J, Guan J, **Wagner WR**: Analysis and design of novel electrospun PEUU scaffolds for soft tissue engineering. *9th Annual Hilton Head Workshop Abstracts* p.30 (2005).

150. Ramaswami P, Guan J, **Wagner WR**: Differentiation factor delivery from a biodegradable elastomer. *9th Annual Hilton Head Workshop Abstracts* p.91 (2005).

151. Nieponice A, Soletti L, Guan J, Huard J, **Wagner WR**, Vorp DA: Preliminary evaluation of a novel muscle-derived stem cell-based vascular construct. *9th Annual Hilton Head Engineered Tissues Workshop Abstracts* p.33 (2005).

152. Guan J, Stankus JJ, **Wagner WR**: Development of elastase-sensitive, biodegradable and flexible scaffolds for soft tissue engineering. *The Regenerate International Conference and Exposition Abstracts,* Abstract A016 (2005).

153. Antaki JF, Diao C, Wu J, Borovetz HS, **Wagner W**, Synder T: Microscopic flow visualization of red blood cell trajectory in the blade tip and back clearance of a mini blood pump. *ASAIO J* 51:6A (2005).

154. Wu J, Antaki JF, Snyder TA, **Wagner WR**, Borovetz HS, Paden BE, Diao C: Elimination of reversal flow in back clearance gaps of a miniature pediatric centrifugal blood pump by CFD. *ASAIO J* 51:40A (2005).

155. Wearden P, Kormos RL, Badylak S, Kameneva MV, Snyder TA, **Wagner WR**, Borovetz HS, Marks JD, Richardson JS, Dasse KA: Evaluation of the Levitronix Centrimag VAS for pediatric use. *ASAIO J* 51:44A (2005).

156. Antaki JF, Wu J, Snyder TA, **Wagner WR**, Borovetz HS, Paden BE, Diao C: CFD analysis of blade tip clearances on hemodynamic performance and blood damage in a miniature pediatric blood pump. *ASAIO J* 51:44A (2005).

157. Wu J, Antaki JF, Bearnson GB, Boston JR, Diao C, Gardiner J, Hawkins JA, Jacobs G, Kameneva MV, Keller BB, Khanwilkar P, Kirk J, Kormos RL, Morell V, Long JW, Li CM, Miles S, Prem E, Paden BE, Paden D, Shaddy RE, Simaan MA, Sydner TA, Tsukui H, Vandenberghe S, **Wagner WR**, Webber SA, Borovetz HS: Progress with Pediaflow Maglev pump for infants and small children: Form to function. *ASAIO J* 51:45A (2005).

158. Vollmer AP, Snyder TA, Kamaneva MV, Monzyk BF, Burckle EC, Dasse KA, Martin PM, Borovetz HS, **Wagner WR**, Gilbert RJ, Thorsen TA: Development of a 2D microfluidic oxygenation device. *ASAIO J* 51:53A (2005).

159. Burgess KA, Yang Q, **Wagner WR**, Federspiel WJ: Development of microfabricated biohybrid artificial lungs. *ASAIO J* 51:53A (2005).

160. Polk AA, McKeel DT, Federspiel WJ, **Wagner WR**: A biohybrid lung prototype with endothelialized microporous hollow fibers in a rotating module. *ASAIO J* 51:55A (2005).

161. Stankus J, Guan J, Fujimoto KL, **Wagner WR**: Fabricating a microintegrated tissue with smooth muscle cells and elastomeric fibers. *Proceedings of the 2005 Biomedical Engineering Society Annual Fall Meeting*, Abstract 63 (2005).

162. Li B, Stankus JJ, **Wagner WR**, Wang JH: Application of polymer/collagen scaffolds to study tendon collagen matrix remodeling. *Proceedings of the 2005 Biomedical Engineering Society Annual Fall Meeting*, Abstract 296 (2005).

163. Guan J, Stankus J, **Wagner WR**: Development of biodegradable and flexible thermosensitive hydrogels for soft tissue engineering. *Proceedings of the 2005 Biomedical Engineering Society Annual Fall Meeting*, Abstract 546 (2005).

164. Courtney T, Sacks M, Stankus J, Guan J, **Wagner W**: Analysis and design of novel electrospun PEUU scaffolds for soft tissue engineering. *Proceedings of the 2005 Biomedical Engineering Society Annual Fall Meeting*, Abstract 1045 (2005).

165. Burgess KA, Hu S, **Wagner WR**, Federspiel WJ: Endothelialization and gas exchange evaluation of biohybrid artificial lung modules. *Proceedings of the 2005 Biomedical Engineering Society Annual Fall Meeting*, Abstract 1144 (2005).

166. Stankus JJ, Guan J, Fujimoto K, **Wagner WR**: Elastomeric tissue mimetics fabricated by a microintegration approach. *AIChE Annual Meeting Conference Proceedings*, p.4301 (2005).

167. Lu E, Kilic S, Bowry S, Wang J, Gretton J, Tom E, **Wagner WR**, Villanueva FS: Targeted echocardiographic imaging of endothelial selectins identifies myocardial ischemic memory. *Circulation* 112:II-501-502 Abstract 2402 (2005).

168. Wang J, Kilic S, Tom E, Lu E, Schellenberger U, Schreiner FG, **Wagner WR**, Villanueva FS: Vascular endothelial growth factor-conjugated ultrasound microbubbles adhere to angiogenic receptors. *Circulation* 112:II-502 Abstract 2404 (2005).

169. Fujimoto KL, Tobita K, Momoi N, Keller BB, Guan J, **Wagner WR**: Elastic, biodegradable cardiac patch induces contractile smooth muscle bundles in sub-acute myocardial infarction, improving cardiac remodeling and function. *Circulation* 112:II-20, Abstract 189 (2005).

170. Polk AA, McKeel DT, Federspiel WJ, **Wagner WR**: A biohybrid lung prototype incorporating rotating, endothelialized microporous hollow fiber bundles. *The Regenerate World Congress on Tissue Engineering and Regenerative Medicine Abstracts,* Abstract 494 (2006).

171. Fujimoto KL, Tobita K, Merryman DW, Momoi N, Guan J, Keller BB, Sacks M, **Wagner WR**: Elastic, biodegradable cardiac patch induces contractile smooth muscle bundles in sub-acute myocardial infarction, improving cardiac remodeling and function. *The Regenerate World Congress on Tissue Engineering and Regenerative Medicine Abstracts,* Abstract 504 (2006).

172. Stankus JJ, Guan J, Fujimoto KL, **Wagner WR**: Smooth muscle cell integrated elastomeric biohybrid matrices. *The Regenerate World Congress on Tissue Engineering and Regenerative Medicine Abstracts,* Abstract 447 (2006).

173. Nieponice A, Deasy BM, Soletti L, Guan J, Huard J, **Wagner WR**, Vorp DA: Evaluation of muscle-derived stem cells within a tissue engineered vascular graft. *The Regenerate World Congress on Tissue Engineering and Regenerative Medicine Abstracts,* Abstract 199 (2006).

174. Courtney T, Liao J, Sacks M, Stankus J, Guan J, **Wagner WR**: Meso- and micromechanics of elastomeric electrospun PEUU scaffolds for cardiovascular tissue engineering. *The Regenerate World Congress on Tissue Engineering and Regenerative Medicine Abstracts,* Abstract 572 (2006).

175. Stankus JJ, Freytes DO, Guan J, Badylak SF, **Wagner WR**: Hybrid fibrous scaffolds from a synthetic elastomer and urinary bladder matrix. *The Regenerate World Congress on Tissue Engineering and Regenerative Medicine Abstracts,* Abstract 606 (2006).

176. Guan J, Huard J, **Wagner WR**: Development of a collagenase-sensitive, flexible scaffold for engineering soft tissues. *The Regenerate World Congress on Tissue Engineering and Regenerative Medicine Abstracts,* Abstract 203 (2006).

177. Guan J, **Wagner WR**: Oriented pore scaffolds from an elastase-sensitive, biodegradable elastomer to achieve mechanical anisotropy and improved cellularization. *The Regenerate World Congress on Tissue Engineering and Regenerative Medicine Abstracts,* Abstract 206 (2006).

178. Ramaswami P, Friz J, Cress D, Guan J, **Wagner WR**: Gene regulation by controlled release from a biodegradable poly(ester urethane)urea. *The Regenerate World Congress on Tissue Engineering and Regenerative Medicine Abstracts,* Abstract 520 (2006).

179. Soletti L, Stankus JJ, Nieponice A, Bacior J, **Wagner WR**, Vorp DA: In-vitro assessment of a biodegradable electrospun vascular graft surface-seeded with muscle-derived stem cells and subjected to shear stress. *The Regenerate World Congress on Tissue Engineering and Regenerative Medicine Abstracts,* Abstract 487 (2006).

180. Stankus JJ, Guan J, Fujimoto KL, **Wagner WR**: Controlled release of bFGF from elastomeric biodegradable microporous sheets. *The Regenerate World Congress on Tissue Engineering and Regenerative Medicine Abstracts,* Abstract 389 (2006).

181. Guan J, **Wagner WR**: Oriented pore scaffolds from an elastase-sensitive, biodegradable elastomer to achieve mechanical anisotropy and improved cellularization. *Transactions of the 31st Annual Meeting of the Society for Biomaterials* 29:376 (2006).

182. Guan J, Huard J, **Wagner WR**: Development of a collagenase-sensitive, flexible scaffold for engineering of urological and other soft tissues. *Transactions of the 31st Annual Meeting of the Society for Biomaterials* 29:24 (2006).

183. Stankus JJ, Freytes DO, Guan J, Badylak SF, **Wagner WR**: Hybrid fibrous scaffolds from a synthetic elastomer and urinary bladder matrix. *Transactions of the 31st Annual Meeting of the Society for Biomaterials* 29:149 (2006).

184. Courtney T, Liao J, Sacks M, Stankus J, Guan J, **Wagner WR**: Micromechanics of electrospun polyester urethane urea scaffolds. *Transactions of the 31st Annual Meeting of the Society for Biomaterials* 29:163 (2006).

185. Stankus JJ, Guan J, Fujimoto K, **Wagner WR**: Controlled release of bFGF from elastomeric biodegradable microporous sheets. *Transactions of the 31st Annual Meeting of the Society for Biomaterials* 29:293 (2006).

186. Snyder TA, Johnson C Jr., Woolley J, Wearden P, Koert A, Richardson S, Dasse K, Borovetz HS, **Wagner WR**: In vivo biocompatibility assessment of a pediatric ventricular assist device. *Transactions of the 31st Annual Meeting of the Society for Biomaterials* 29:531 (2006).

187. Wearden P, Morell V, Badylak S, Kameneva MV, Snyder TA, Bengston S, **Wagner WR**, Borovetz HS, Koert AJ, Gempp T, Gellman BN, Dasse KA: Development and in vivo evaluation of the Levitronix pediatric VAS. *ASAIO J* 52:34A (2006).

188. Johnson CA Jr, Snyder TA, Woolley JR, **Wagner WR**: Development of flow cytometric assays for biocompatibility assessment in ovines. *ASAIO J* 52:38A (2006).

189. Woolley JR, Snyder TA, Johnson CA Jr, **Wagner WR**: Functional platelet and heparin activity assays applied to ovines. *ASAIO J* 52:48A (2006).

190. Antaki J, Arnold D, Bachman T, Bearnson G, Borovetz H, Gardiner J, Donachy J, Drummond A, Johnson C, Kameneva M, Keller B, Kirk J, Kormos R, Maher T, Morell V, Paden B, Paden D, Ricci M, Shu F, Snyder T, Shaun S, Vandenberghe S, **Wagner W**, Verkaik J, Wearden P, Weber S, Wooley J, Wu J: Optimization, validation, and re-optimization of Pedia-Flow maglev turbo-VAD. *ASAIO J* 52:56A (2006).

191. Snyder TA, Johnson CA Jr, Woolley JR, Wearden PD, Koert AJ, Dasse KA, Borovetz HS, **Wagner WR**: Biocompatibility evaluation of the Levitronix pediatric VAD in ovines. *ASAIO J* 52:58A (2006).

192. Polk AA, McKeel DT, Federspiel WJ, **Wagner WR**: A biohybrid lung prototype with active mixing and oxygenation of endothelialized microporous hollow fibers. *ASAIO J* 52:67A (2006).

193. Courtney T, Liao J, Stankus J, Guan J, **Wagner W**, Sacks M: Micromechanics of electrospun poly ester urethane urea scaffolds for soft tissue engineering. *J Biomech* 39,S1:S262 (2006).

Other Publications:

Griffith BP, **Wagner WR**: Invited commentary on "A novel organ culture method to study intimal hyperplasia at the site of a coronary artery bypass anastomosis" by DelRizzo DF et al. *Ann Thorac Surg* 71:1279-1280 (2001).

Wagner WR: Biochemical and biophysical mechanisms of mural thrombosis on natural surfaces. Dissertation for Doctor of Philosophy, University of Texas at Austin, pp 148, (1991).

Wagner WR: Welcome to Acta Biomaterialia. *Acta Biomaterialia* 1:3-4 (2005).

Wagner WR: Preface to the third issue. *Acta Biomaterialia* 1:253 (2005).

PROFESSIONAL ACTIVITIES

TEACHING:

Courses Taught:

BIOE 2810 **Biomaterials and Biocompatibility**

This course provides and introduction to biomaterials science and engineering and biocompatibility. The first half of the semester is materials science and polymer chemistry oriented while the second is physiologically oriented. Until 2004 this course was comprised of senior Bioengineering and Chemical Engineering undergraduates and first year Bioengineering graduate students. In 2004 the course was split into undergraduate and graduate sections, the latter being BIOE 2810.

28 lectures, approximately 40 contact hours.
(New course, not previously offered)

Fall 1997	11 students
Fall 1998	15 students
Spring 2000	19 students
Spring 2001	26 students
Spring 2002	36 students
Spring 2003	35 students
Spring 2004	40 students
Spring 2005	18 students
Spring 2006	10 students
Spring 2007	19 students

BIOE 2220/CHE 2220 Cardiovascular Biomaterials and Tissue Engineering

Prior to 1999 this course covered cardiovascular biomaterials and blood-contacting medical devices. In 1999 the course moved to an emphasis on tissue engineering principles in the cardiovascular system. The course is designed as an advanced graduate course and requires a previous biomaterials course. There are substantial literature review and discussion components.

28 lectures, approximately 40 contact hours.
(New course, not previously offered)

Spring 1996	7 students
Spring 1997	13 students
Spring 1998	8 students
Spring 1999	2 students
Fall 1999	5 students
Fall 2001	11 students
Fall 2003	7 students

BIOE 2520 Molecular Cell Biology and Biophysics I

This course is required of all first year Bioengineering graduate students and provides an overview of molecular biology. Dr. Wagner is responsible for the first section of the course, which covers biochemistry fundamentals.

4 lectures, approximately 6 contact hours

(New course, not previously offered)

Spring 2004	46 students
Fall 2004	35 students
Fall 2005	37 students
Fall 2006	35 students

BIOE 2023 **Bioengineering Graduate Seminar Series**

This was the departmental seminar series that brought in external speakers once a week.

Fall 2000	14 students
Spring 2001	41 students
Fall 2001	43 students
Spring 2002	47 students

BIOE 2051 **Heat and Mass Transfer in Biological Systems**

This graduate course covered the application of heat and mass balance equations to biological systems with an emphasis on derivations and numerical problem solving. Dr. Wagner covered most of the mass transfer aspects of the course.

8 lectures, approximately 12 contact hours
(New course, not previously offered)

Spring 1994	14 students

BIOE 2010 **Bioprinciples II: Biomaterials**

This half-semester course provided an introduction to biomaterials and biocompatibility and was required for all first year Bioengineering graduate students. After 1996 a full semester biomaterials course was developed.

14 lectures, approximately 20 contact hours.
(New course, not previously offered)

Fall 1993	16 students
Fall 1994	16 students
Fall 1995	13 students
Fall 1996	16 students

CHE 3002 **Chemical Engineering Graduate Seminar Series**

This was the departmental seminar series that brought in external speakers once a week.

Spring 1996	20 students (estimate)

Fall 1996 20 students (estimate)

BIOE 2022/CHE 2125 Cardiovascular Dynamics and Blood-Material Interactions

This course combined cardiovascular fluid dynamics principles with cardiovascular device and biomaterial issues. Dr. Wagner taught the half of the course dealing with cardiovascular devices and biomaterials. After 1995 this course developed into a full semester advanced graduate course on cardiovascular biomaterials.

14 lectures, approximately 20 contact hours.
(New course, not previously offered)

Fall 1993 10 students
Spring 1995 11 students

Guest Lectures:

- **BIOE 2010** – Bioprinciples I (1992, 1993) *Topic:* Diffusion
- **BIOE/CHE 1531** – Fundamentals of Biochemical Engineering (1994) *Topic:* Protein Folding
- **CHE 2756** – Polymerization Engineering (2000) *Topic:* Polymer Biocompatibility
- **BIOE 1210** – Bioengineering Thermodynamics (2003) *Topic:* The Thermodynamics of Protein Adsorption
- **BIOE 2072** – Functional Tissue Engineering: The Biomechanics of Tissue Design (2003) *Topic:* Scaffolds for Soft Tissues
- **PHARM 3008** – Advanced Drug Delivery and Targeting (2003, 2006) *Topic:* Hydrogels and Tissue Engineering
- **BIOE 3015** – Scaffolds for Regenerative Medicine (2006) *Topic*: Polyester and Polyurethane Scaffolds for Tissue Engineering

Current Doctoral Candidates:

Priya Ramaswami, Bioengineering Department, University of Pittsburgh (project: Biomaterial guided stem cell differentiation). Expected graduation date: December 2007.
2003, 2005 – MIGS-Net (Local Graduate Student Organization) National Meeting Travel Awards
2004 - Second Place, Graduate Student Presentations, Annual Department of Pathology Retreat

Carl A. Johnson, M.D./Ph.D. candidate, Bioengineering Department, University of Pittsburgh (project: Biocompatibility analysis of a pediatric ventricular assist device). Expected graduation date: September 2008.
2003 - Gordon Research Conferences Travel Fellowship (Assisted Circulation Conference)
2004 - University of Pittsburgh School of Engineering Dean's Fellowship

2006 – Outstanding Poster Presentation in Group, ASAIO Annual Conference

Joshua R. Woolley, Bioengineering Department, University of Pittsburgh (project: Ovine models for cardiovascular device biocompatibility testing). Expected graduation date: September 2010.

Nicholas J. Amoroso, Bioengineering Department, University of Pittsburgh (project: Elastomeric scaffold development for soft tissue engineering). Expected graduation date: September 2010.

Completed Doctorates:

Christopher R. Deible, M.D./Ph.D. (1998), Bioengineering Department, University of Pittsburgh. Dissertation: "*Molecular barriers to thrombosis formed with protein reactive polyethylene glycol*". Current position: Assistant Professor of Radiology, University of Pittsburgh.
1995-1997 - Pre-doctoral Fellowship, American Heart Association

Richard D. Schaub, Ph.D. (1999), Bioengineering Department, University of Pittsburgh. Dissertation: "*Development of a novel fiber optic probe for blood cell visualization*". Current position: Clinical Research Coordinator, Artificial Heart Program & Adjunct Assistant Professor of Bioengineering, University of Pittsburgh.
1995 - First Place, Biomedical Engineering Society (Univ. of Pittsburgh) Symposium
1997 - National Institutes of Health T32 Training Fellowship
1997 - International Society for Artificial Organs Travel Grant
1997 - Koyanagi Young Investigator Award, International Society For Rotary Blood Pumps
1998 - ASAIO Biomedical Engineering Student Fellowship Award

Carl R. Wilhelm, Ph.D. (2000), Bioengineering Department, University of Pittsburgh Dissertation: "*Mechanisms of thromboembolism in ventricular assist device patients*". Current position: Clinical Science Manager for Abbott Laboratories.

Gregory E. Weller, M.D./Ph.D. (2003), Bioengineering Department, University of Pittsburgh Dissertation: "*Development and characterization of ultrasound contrast media targeted to dysfunctional cardiovascular tissue*". Current position: Resident in Anesthesiology & Critical Care Medicine at the University of Pennsylvania.
1999-2000 - Pre-doctoral Fellowship, American Heart Association, Mid-Atlantic Affiliate
2003 - First Place, American Heart Association Fellows' Research Day

Kenneth L. Gage, (M.D.)/Ph.D. (2005), Chemical Engineering Department, University of Pittsburgh, Dissertation: "*Development of computational mass and momentum transfer models for extracorporeal hollow fiber membrane oxygenators*". Current position: Third year medical student, University of Pittsburgh.
1998 – Best Graduate Student Poster, Univ. of Pittsburgh BMES Student Symposium

1998 – Biomedical Engineering Student Fellowship, American Society for Artificial Internal Organs
1998-2002 – Computational Science Graduate Fellowship, Krell Institute, U.S. Department of Energy
1999 – Wellington C. Carl Engineering Scholarship, Department of Chemical Engineering
2001 – Coro Pittsburgh Health Sciences Fellowship, Jewish Healthcare Foundation and Coro Center for Civic Leadership
2002 – Best Senior Graduate Student Poster, MD/PhD Program Retreat

Timothy E. Deglau, Ph.D. (2005) Bioengineering Department, University of Pittsburgh
Dissertation: *"Surface modified vascular tissue for targeted drug delivery"*.
Current position: Senior Field Clinical Engineer, Medtronic Corp.
2000- Travel Fellowship, Biomedical Engineering Society Annual Meeting
2000 - ASAIO Biomedical Engineering Student Fellowship
2003 - McGowan Institute for Regenerative Medicine Retreat Poster Award

Trevor A. Snyder, Ph.D. (2006) Bioengineering Department, University of Pittsburgh
Dissertation: *"Preclinical biocompatibility assessment of cardiovascular devices"*, Current position: Post-doctoral researcher, University of Pittsburgh
2002 - First place, Malchesky ASAIO Student Abstract Competition
2003 - First place, Society for Biomaterials Cardiovascular Biomaterials Special Interest Group Student Abstract Competition

John J. Stankus, Ph.D. (2006) Chemical Engineering Department, University of Pittsburgh
Dissertation: *"Functional elastomeric scaffold development for tissue engineering"*, Current position: Research scientist, Guidant Corp.
2001 – Dean's Fellowship
2002 – Pennsylvania Space Grant Consortium Fellowship
2002-2004 - NIH (T32) Biotechnology Training Fellowship,
2004 - McGowan Institute Travel Award
2004 – McGowan Institute for Regenerative Medicine Retreat Poster Award

Alexa A. Polk, Ph.D. (2006) Bioengineering Department, University of Pittsburgh
Dissertation: "*Development of a biohybrid lung*", Current position: Clinical engineer, Sacred Heart Medical Center, Spokane, WA
2001 - Student Travel Award, ASAIO Annual Conference
2003 - MIGS-Net (Local Graduate Student Organization) National Meeting Travel Award
2003-2004 - NIH "CATER" T32 Fellow
2005–2006 - University of Pittsburgh Provost's Fellow
2005 - Student Travel Award, ASAIO Annual Conference

Visiting Graduate Student:

Lorenza Draghi (2004-2005) Dipartimento di Bioingegneria, Politecnico di Milano, Italy, (project: Electrospinning polymer blends into small diameter tissue engineering conduits).

Completed Master's Students :

Hudson Tiffany, M.S. (1995), Bioengineering Program, University of Pittsburgh (thesis: Surface bound thrombin on preclotted Dacron vascular grafts mediates platelet deposition).

Ronald J. Jankowski, M.S. (1997), Bioengineering Program, University of Pittsburgh (thesis: The effect of retroviral transduction on human endothelial cell phenotype and adhesion to Dacron vascular grafts).

Celeste J. Powell, M.S. (1997), Chemical Engineering Department, University of Pittsburgh (thesis: Covalent attachment of epidermal growth factor and gly-arg-gly-asp to surfaces to promote cell adhesion and spreading).

Linda C. Baker, M.S. (1997), Chemical Engineering Department, University of Pittsburgh (thesis: Flow cytometric assays to detect platelet activation and microaggregates in device implanted calves).

Janice Panza, M.S. (1997), Chemical Engineering Department, University of Pittsburgh (thesis: Strategies for covalent modification of the islets of Langerhans for possible immunoisolation).

Susan J. Dadd, M.S. (1999) Chemical Engineering Department, University of Pittsburgh (thesis: Characterization of pancreatic islet modification with amine-reactive polyethylene glycol).

Carl L. Engman, M.S. (2002), Bioengineering Department, University of Pittsburgh (thesis: Immunoprotection of pancreatic islets by covalent modification with PEG).

Service on Graduate Committees:

Ph.D.:

1. Danny O. Freytes (Ph.D., Bioengineering, Stephen Badylak, Advisor)
2. Jolene E. Valentin (Ph.D., Bioengineering, Stephen Badylak, Advisor)
3. Timothy M. Maul (Ph.D., Bioengineering, David Vorp, Advisor)
4. Kyle G. Grant (Ph.D., Chemical Engineering, Mohammad Ataai, Advisor)
5. Robert G. Svitek (Ph.D., Chemical Engineering, William Federspiel, Advisor)
6. Mohammed El-Kurdi (Ph.D., Bioengineering, David Vorp, Advisor)
7. George C. Engelmayr, Jr. (Ph.D., Bioengineering, Michael Sacks, Advisor)
8. Bridget M. Deasy (Ph.D., Bioengineering, Johnny Huard, Advisor)
9. Susan K. Maleckar (Ph.D., Chemistry, Toby Chapman, Advisor)
10. Pamela Y. Meadows (Ph.D., Chemistry, Gilbert Walker, Advisor)
11. Mariah S. Hout (Ph.D., Bioengineering, William Federspiel, Advisor)

12. Kristie Henchir-Burgess (Ph.D., Bioengineering, William Federspiel, Advisor)
13. Scott VanEpps (Ph.D., Bioengineering, David Vorp, Advisor)
14. Lorenzo Soletti (Ph.D., Bioengineering, David Vorp, Advisor)
15. Wesley Sivak (Ph.D., Bioengineering, Eric Beckman, Advisor)
16. Thomas Payne (Ph.D., Bioengineering, Johnny Huard, Advisor)
17. Ronald J. Jankowski (Ph.D., Bioengineering, Johnny Huard, Advisor)
18. Suzanne Castilla (Ph.D., Bioengineering, David Vorp, Advisor)
19. Peter Pediaditakis (Ph.D., Pathology, George Michalopoulos, Advisor)
20. James B. Wechuck (Ph.D., Chemical Engineering, Mohammad Ataai, Advisor)
21. Erik N. Sorensen (Ph.D., Bioengineering, James Antaki, Advisor)
22. Janine M. Orban (Ph.D., Chemistry, Toby Chapman, Advisor)
23. Laura W. Lund (Ph.D., Bioengineering, William Federspiel, Advisor)
24. Stephanie M. Kute (Ph.D., Bioengineering, David Vorp, Advisor)
25. David Wang (Ph.D., Bioengineering, David Vorp, Advisor)
26. Fotios M. Andreopoulos (Ph.D., Bioengineering, Alan Russell, Advisor)

External Ph.D. Examiner:

27. Mark J. Ernsting, Ph.D., Graduate Department of Chemical Engineering and Applied Chemistry, University of Toronto, Toronto, Canada, April 2005 (J. Paul Santerre, Advisor)
28. Cecelia Alperin, Graduate Department of Chemical Engineering and Applied Chemistry, University of Toronto, Toronto, Canada, January 2007 (Kimberly A. Woodhouse, Advisor)

Master's:

29. Nicolas A. Perrusquia (M.S., Bioengineering, Ken Fischer, Advisor)
30. Ahmed Nadeem (M.S., Bioengineering, James Antaki, Advisor)
31. Yi J. Miao (M.S. Bioengineering, Jun-Kyo Suh, Advisor)
32. Brian A. Russell (M.S., Chemical Engineering, Mohammad Ataai, Advisor)
33. James R. Kneller (M.S. Bioengineering, Harvey Borovetz, Advisor)
34. Kimberly A. Dezura (M.S., Chemical Engineering, Mohammad Ataai, Advisor)
35. Gary A. Jesionowski (M.S., Chemical Engineering, Mohammad Ataai, Advisor)

External Bachelor's Thesis:

36. Dina Basalyga, Undergraduate Chemistry Thesis, Chatham College, Pittsburgh, PA, (William Wagner and Flordeliza Villanueva, Faculty Advisors)

Post-Doctoral and Research Fellow Supervision:

Haiyan Xu, Ph.D. (1999-2000) Visiting Faculty Fellow, Peking Medical College (project: Characterization of proteins modified with poly(ethylene glycol)).

Jianjun Guan, Ph.D. (2000-2005) Post-Doctoral Associate (project: Biodegradable polyurethanes for tissue engineering).

Hideki Oshima, M.D. (2001-2004) Post-Doctoral Associate (co-advisor), (project: Muscle-derived stem cells for cardiac tissue engineering).

Kazuro Fujimoto, M.D. (2002-current) Post-Doctoral Associate (project: Living tissue for congenital cardiac reconstruction).

Er-Xiong Lu, M.D. (2000-2005) Post-Doctoral Associate (co-advisor), (project: Targeted ultrasound contrast to detect cardiac allograft rejection).

Yu Liu, M.D. (2002-2003) Post-Doctoral Associate (project: Intravascular targeted delivery of microspheres).

Matundu Felix, Ph.D. (2002-2004) Post-Doctoral Associate (co-advisor), (project: Development of targeted ultrasound contrast agents).

Jianjun Wang, Ph.D. (2005-current) Post-Doctoral Associate (co-advisor), (project: Targeting ultrasound contrast agents to angiogenic vascular beds).

Yi Hong, Ph.D. (2006-current) Post-Doctoral Associate (project: Biodegradable scaffolds for cardiovascular tissue engineering).

Xin Fan, Ph.D. (2006) Post-Doctoral Associate (co-advisor), (project: Ultrasound contrast agent agent development).

Sang Ho Ye, Ph.D. (2006-current) Post-Doctoral Associate (project: Surface modification for improved blood biocompatibility of pediatric ventricular assist devices).

Mustafa Kocakulak, Ph.D. (2006-current) Post-Doctoral Associate (project: Biocompatibility analysis of an extracorporeal device for the removal of select cytokines from septic patients).

Undergraduate Research Supervision:

- Undergraduates and medical students from 26 different academic institutions (for at least one semester each). Funding included National Science Foundation, Research Experiences for Undergraduates (REU) grant through Chemical Engineering Department, Pittsburgh Tissue Engineering Summer Intern Program, Carnegie-Mellon University Summer Opportunities in Biomedical Engineering Program.

1992

1) Michael Chang (Chemical Engineering, Carnegie-Mellon University)
2) Elizabeth Joyce (Chemical Engineering, Carnegie-Mellon University)

1993

3) Angela Chang (Chemical Engineering, Carnegie-Mellon University)

4) Sarah Hamilton (Chemical Engineering, Carnegie-Mellon University)
5) Julie Hickman (Chemical Engineering, Case Western Reserve University)
6) Stacy Krisher (Medicine, University of Pittsburgh)

1994
7) Stephanie Stine (Chemical Engineering, Carnegie-Mellon University)
8) Heather Kos (Chemical Engineering, Case Western Reserve University)
9) Ian Baxter (Biology, California University of Pennsylvania)
10) Sharon J. Morgan (Chemical Engineering, Carnegie-Mellon University)

1995
11) Tim Deglau (Chemical Engineering, Carnegie-Mellon University)
12) Adam Cody (Chemical Engineering, Carnegie-Mellon University)
13) Stephen Yang (Biochemistry, Rice University)
14) Christine Rice (Biology, California University of Pennsylvania)
15) Art Thomas (Chemical Engineering, Bucknell University)
16) Preeti Patheja (Biology, University of Michigan)
17) Christopher Chen (Medicine, University of Pennsylvania)
18) Duane Wright (Chemical Engineering, University of Pittsburgh)
19) Niral Patel (Biology, University of Pittsburgh)

1996
20) Amanda Lydic (Chemical Engineering, University of Pittsburgh)
21) Towanda Terrell (Chemical Engineering, University of Pittsburgh)
22) Nelson Bennett (Medicine, University of Pittsburgh)
23) Ken Gage (Medicine, University of Pittsburgh)
24) Chris Levins (Materials Science, University of Pittsburgh) and 1997, 1998
25) Jaqueline Autieri (Chemical Engineering, Carnegie-Mellon University)
26) Ryan Miller (Chemical Engineering, University of Dayton)
27) Ian Connor (Chemical Engineering, West Virginia University)
28) Pace Markowitz (Chemical Engineering, University of Pittsburgh)
29) Curtis Miller (Physics, University of Pittsburgh)
30) Tuan Lu (Chemical Engineering, University of Pittsburgh)

1997
31) Jim Kim (Medicine, University of Pittsburgh)
32) Spencer Tseng (Medicine, University of Pittsburgh)
33) Derek Cissell (Chemical Engineering, Carnegie-Mellon University)
34) Therese McCullough (Chemical Engineering, Gannon University)
35) Sridharan Raghavan (Chemical Engineering, Massachusetts Institute of Technology)
36) Dina Basalyga (Chemistry, Chatham College) and 1998

1998
37) Rachelle Abati (Chemical Engineering, Carnegie-Mellon University)
38) Claudia Grossman (Biology, Washington University)
39) Jonathan Bickel (Biology, Earlham College)

40) Aisha Moore (Materials Science, Carnegie-Mellon University)
41) Amalia Morsii (Bioengineering, University of Pittsburgh)

1999
42) Andre Gentil (Medicine, University of Sao Paulo)
43) Nicole Price (Bioengineering, University of Pittsburgh)
44) Tim Duval (Chemical Engineering, University of Pittsburgh)
45) Carl Johnson (Chemical Engineering, Michigan State Univ.) and 2003 as medical student
46) Tamla Simmons (Biology, Hampton University)
47) Maret Birru (post-secondary, pre-university)
48) Peter Hurh (Biology, University of Virginia)
49) Stephanie Sapp (Chemical Engineering, University of Pittsburgh)
50) Tom Robey (Bioengineering, University of Pittsburgh) and 2000
51) Anika Joseph (Bioengineering, University of Pittsburgh)
52) Robert Svitek (Bioengineering, University of Pittsburgh)

2000
53) Michael Patterson (Bioengineering, University of Pittsburgh)
54) Neshat Rowghani (Chemical Engineering, University of Pittsburgh)
55) Katrina Dobbs (Chemical Engineering, University of Pittsburgh)
56) Nicole White (Biology, Hampton University)
57) Rebecca Nick (Chemistry, Gannon University)
58) Eric Miller (Chemical Engineering, Carnegie-Mellon University)
59) Brian Modina (Mechanical Engineering, Virginia Tech)
60) Brian Fill (Bioengineering, University of Pittsburgh)
61) Christy Wright (Bioengineering, University of Pittsburgh)

2001
62) Kristina Goodoff (Bioengineering, University of Pittsburgh)
63) Diana Yoon (Chemical Engineering, Carnegie-Mellon University)
64) Kendra Krutilla (Chemical Engineering, University of Pittsburgh) and Fall 2001
65) Samer Melhem (Biomedical Engineering, Duke University)
66) John Stankus (Chemical Engineering, University of Pittsburgh)
67) Melissa Jacubzak (Bioengineering, University of Pittsburgh)
68) Marina Udowenko (Bioengineering, University of Pittsburgh)
69) Kim Karavitch (Bioengineering, University of Pittsburgh)

2002
70) Margrit Rosado (Chemical Engineering, Carnegie-Mellon University)
71) Vishal Patel (Bioengineering, University of Pittsburgh)
72) Martha Ottenburg (Chemical Engineering, Carnegie-Mellon University)
73) Leah Henderson (Chemistry/Math, Lincoln University)
74) Adam Pfeiffer (Chemical Engineering, Colorado State University)
75) Mihoko Hashimoto (Bioengineering, University of Pittsburgh) and 2003
76) Melissa Nervo (Bioengineering, University of Pittsburgh)
77) Kimberly Albrecht (Bioengineering, University of Pittsburgh) and 2003, 2004

2003
78) Jim Culhane (Chemical Engineering, University of Pittsburgh)
79) Amber Mazzoccoli (Chemical Engineering, University of Pittsburgh)
80) Tamika Perry (Chemical Engineering, Carnegie-Mellon University)
81) Mary Pham (Chemical Engineering, Kansas State University)
82) Selena Daniels (Biomedical Engineering, New Jersey Institute of Technology)
83) Hann-Chung (Ed) Wong (Chemical Engineering, Carnegie-Mellon University)
84) Hiroki Meguro (Bioengineering, University of Pittsburgh)
85) Andres Correa (Bioengineering, University of Pittsburgh)

2004
86) Michael Callahan (Bioengineering, University of Pittsburgh)
87) Eric Schoch (Bioengineering, University of Pittsburgh)
88) Jermaine Johnson (Bioengineering, University of Pittsburgh) and 2005
89) Bradley Lomago (Bioengineering, University of Pittsburgh)
90) Christian Yeasted (Biology, John Carroll University)
91) Michael Strahota (Bioengineering, University of Pittsburgh)
92) Michael Audette (Bioengineering, University of Pittsburgh)
93) Morgan Carpenter (Bioengineering, University of Pittsburgh) and 2005

2005
94) Daqian Wu (Chemical Engineering, Carnegie-Mellon University)
95) Nathan Angeloff (Bioengineering, University of Pittsburgh)
96) Craig Lehocky (Bioengineering, University of Pittsburgh)
97) Nick Amoroso (Bioengineering, Case Western Reserve University)
98) Jamie Costabile (Bioengineering, University of Pittsburgh)

2006
99) Amber Loree (Bioengineering, University of Pittsburgh)
100) Kevin Affum (Biochemistry, University of Maryland)
101) Erin Wacker (Bioengineering, University of Pittsburgh)
102) Summit Kundaria (Medicine, University of Pittsburgh)
103) Kyra Ceceris (Bioengineering, University of Pittsburgh)
104) Evan Hill (Bioengineering, University of Pittsburgh)

RESEARCH:

Current Grant Support:

SOURCE/ GRANT NUMBER	GRANT TITLE	ROLE IN PROJECT AND % EFFORT	YEARS INCLUSIVE	DIRECT DOLLARS	INDIRECT DOLLARS

NIH / HL069368	Cardiopulmonary Organ Engineering	P.I. 30% effort	7/03-6/08	3,604,517	1,404217
Commonwealth of PA / Grant # pending	Oxygen Transfer Characteristics of a Biohybrid Lung	P.I. 5% effort	7/05-6/06	62,870	6,287
NIH / HL080926	Systems Engineering of Pheresis Intervention for Sepsis (J. Kellum, PI)	Co-Inv 8% effort	4/05-3/10	5,389,029	1,826,009
NIH / HL069956	Design of Extracorporeal Specific Antibody Filters (W. Federspiel, PI)	Co-Inv 5% effort	9/03-8/07	1,000,000	417,346
US Army / DAMD 17-02-1-0717	National Tissue Engineering Center- Biodegradable Elastomeric Scaffolds for Fasciotomy Management and Repair	P.I. of listed project 5% effort	10/04-9/06	141,904	58,096
NIH / HL58865	Echocardiographic Evaluation of Endothelial Function (F. Villanueva, PI)	Co-Inv 5% effort	07/02-6/07	900,000	367,367
NIH / HL077534	Targeted Ultrasound Imaging of Angiogenic Receptors (F. Villanueva, PI)	Co-Inv 5% effort	07/04-06/08	1,000,000	825,393
NIH / N01-HV-48192	Pediatric Circulatory Support (H. Borovetz, PI)	Co-Inv 8% effort	03/04-03/09	3,350,219	466,275
NIH / HL77028	Circulatory Support Device for Toddlers/Small Children (J. Antaki, PI)	Co-Inv 4% effort	07/04-07/06	152,383	47,332
NIH / N01-HV-48192	Minority Graduate Research Supplement-Pediatric Circulatory Support (Carl Johnson)	Supervisor	09/04-03/09	109,039	52,339
NIH / HL071376	Development of a Magnetically Driven Heart Pump (K. Dasse, PI)	Co-Inv 5% effort	02/05-01/07	364,073	86,688
US Army / DAMD 17-02-1-0717A	National Tissue Engineering Center- Biodegradable Elastomeric Scaffolds for Temporary Closure of Abdominal Wall in Damage Control Laparotomy	P.I. of listed project 10% effort	10/05-9/06	139,770	60,230

NIH / EB00424	Engineering Structural Tissues for Clinical Medicine, T32 (R. Rubin, PI)	Training Faculty	9/02-6/07
NIH / GM65100	Biotechnology Training Grant, T32 (M. Ataai, PI)	Training Faculty	7/03-6/08
NIH / EB01026	Cellular Approaches to Tissue Engineering/Regeneration, T32 (A. Russell, PI)	Training Faculty	7/03-4/08
NIH / HL76124	Cardiovascular Bioengineering Training Program, T32 (S. Shroff, PI)	Training Faculty	8/05-7/10
NIH / EB03392	Training in Biomechanics in Regenerative Medicine, T32 (M. Sacks, PI)	Training Faculty	8/05-7/10
NIH / GM08208	Medical Scientist Training Program, T32 (C. Wiley, PI)	Training Faculty	7/02-6/07

Prior Grant Support:

SOURCE/ GRANT NUMBER	GRANT TITLE	ROLE IN PROJECT AND % EFFORT	YEARS INCLUSIVE	DIRECT DOLLARS	INDIREC DOLLAR
NIH / HL70051	Percutaneous Respiratory Assist Catheter (W. Federspiel, PI)	Co-Inv 5% effort	04/02-03/07	1,000,000	447,962
NIH/ HL040962	Biobehavioral Studies of Cardiovascular Disease (S. Manuck, PI)	Co-Inv 5% effort	3/01-2/07	904,000	452,000
NIH/DE007336	Short-Term Dental Student Research Program, T35 (M. Mooney, PI)	Training Faculty	3/01-2/06		
Commonwealth of PA / SAP# 4100023829	Biohybrid Lung and Micro-integrated Tissue Engineered Blood Vessel	P.I. 10% effort	7/04-6/05	124,707	12,471
NIH / MH052247	Intervention Research Center for the Study of Late-Life Mood Disorder (C. Reynolds, PI)	Co-Inv 5% effort	3/00-2/05	8,121,693 (total costs)	

US Army / Log#03029002	National Tissue Engineering Center – Targeted Cardiovascular Drug Delivery	P.I. of listed project 5% effort	10/02-7/05	140,000	
NIH / HL58617	Molecular Barriers to Thrombosis on Tissue Surfaces	P.I. 30% effort	9/98-8/04	350,000	165,600
American Heart Association / 0140064N	Development of Targeted Ultrasound Contrast Agents for the Echocardiographic Assessment of Endothelial Function (F. Villanueva, PI)	Co-Inv 5% effort	1/01-12/04	272,728	27,272
NIH / HL065740	Development of a Chronic Artificial Lung (B. Griffith, PI)	Co-Inv 25% effort	7/00-5/04	2,488,551	1,200,756
Whitaker Foundation	Support for a Gordon Research Conference on Biomaterials: Biocompatibility & Tissue Engineering	P.I.	3/03-8/03	8500	
American Medical Association Foundation	Creation of vascularized tissue engineered cardiac patch using omentum (Tetsuro Sakai)	Supervisor	1/03-12/03	2500	
Commonwealth of PA / ME01-254	Materials for Tissue Engineered Scaffolds, Development of a Biohybrid Lung, and Living Tissue for Cardiac Reconstruction in Congenital Heart Defects	P.I. of listed projects 50% effort	7/01-6/03	299,000	
The Pittsburgh Foundation / A 2000-0461	Biohybrid Organ Development	P.I. 20% effort	7/01-7/03	180,000	
Dept. of Energy / Krell Institute	Computational Science Graduate Fellowship (Kenneth Gage)	Supervisor	9/98-8/02	76,000	
Pittsburgh Tissue Engineering Initiative / 3046735	Cell Therapy for Congestive Heart Failure Using Skeletal Muscle-Derived Stem Cells	P.I. 5% effort	7/01-7/02	50,000	
Mallinckrodt Medical / 700289	Development of Targeted Imaging Agents (F. Villanueva, PI)	Co-Inv	4/99-4/02	93,778	32,822

Pittsburgh Tissue Engineering Initiative / 2450235	Toward a Tissue Engineered Lung	P.I. 10% effort	7/00-12/01	50,000	
American Heart Association	Development and Characterization of Ultrasound Contrast Agents Targeted to Dysfunctional Endothelium (Pre-Doctoral Fellowship, Gregory Weller)	Supervisor	7/99-6/01	32,000	
American Heart Association	Cell Therapy for Congestive Heart Failure Using Skeletal Muscle-Derived Stem Cells (Tetsuro Sakai, Post-doctoral Fellowship)	Supervisor	Awarded, but returned when fellow was admitted to residency program 7/01		
NIH / HL58865	Echocardiographic Study of the Coronary Microvasculature (F. Villanueva, PI)	Co-Inv 10% effort	8/97-6/01	280,000	140,350
The Whitaker Foundation	Innovations in Bioengineering Education, Development Award (J. Schultz, PI)	Co-Inv, Training Faculty	7/97-6/01	3,000,000	
The Pittsburgh Foundation	Development of Immunoisolative Barriers on Pancreatic Islets to Mediate Cellular Transplantation	P.I. 20% effort	9/97-8/00	150,000	
Army Medical Research and Materiel Command	Continued Development of the Intravenous Oxygenator (B. Hattler, PI)	Co-Inv	7/98-6/00	1,497,660 (total cost)	
Mallinckrodt Medical	Development of Targeted Contrast Agents for Ultrasound Imaging (F. Villanueva, PI)	Co-Inv	7/98-6/00	45,000	
NIH / HL56499	Improved Hollow Fibers for Intravenous Blood Oxygenators, Phase II SBIR (D. Friesen, PI)	Co-Inv 5% effort	2/98-1/00	268,575 (University subcontract)	
NIH / HL58155	Development of an Innovative Ventricular Assist System (K. Butler, PI)	Co-Inv 10% effort	9/95-9/00	2,670,000 (University subcontract)	

Forest Laboratories / CIT-MD3-97-03-000	Platelet Activation in a Randomized Double-Blind Placebo-Controlled Trial of Citalopram in Depressed Patients at Least 75 Years of Age	P.I.	5/98-6/00	21,700
Pittsburgh Tissue Engineering Initiative	Model Systems for Pancreatic Islet Modulation (G. Block, PI)	Co-Inv 5% effort	7/98-6/99	50,000 (total cost)
NIH / HL52997	Improved Efficiency Extracorporeal Membrane Oxygenators, Phase II SBIR (S. Nemser, PI)	Co-Inv 5% effort	9/97-8/99	749,824 (total cost)
NIH / HL54295	Axial Flow Blood Pump with Simplified Bearings – Phase II SBIR (K. Butler, PI)	Co-Inv 5% effort	12/96-9/98	361,113
NIH / HL51667	Pediatric Blood Pump Development – Phase II SBIR (K. Butler, PI)	Co-Inv 5% effort	5/96-7/98	304,198
The Whitaker Foundation	Program Enhancement in Bioengineering: Clinical Cardiovascular Bioengineering (H. Borovetz, PI)	Co-Inv 15% effort	9/95-8/98	748,954
NIH / GM08540	Biotechnology of Genes and Proteins, T32 Biotechnology Training Grant (J. Schultz, PI)	Training Faculty	1/94-6/98	1,600,000
Datascope Corp.	Evaluation of Fibrillar Hemostatic Agents	P.I.	9/97-8/98	4,980
American Heart Association	Mechanisms of Thromboembolism in Ventricular Assist Device Patients (National Grant-in-Aid)	P.I. 25% effort	7/95-6/98	100,100
The Whitaker Foundation	Computational Fluid Dynamics and Quantitative Image Analysis Applied to Membrane Oxygenator Design	P.I. 30% effort	7/95-6/98	209,295
Cohesion Corp.	Tissue Adhesive Hemostatic Activity	P.I.	7/96-6/97	22,000

American Heart Association	Covalent Modification of the Luminal Surface of Coronary Arteries with Polyethylene Glycol Following Balloon Angioplasty (Pre-Doctoral Fellowship, Christopher Deible)	Supervisor	7/95-6/97	20,000
Ben Franklin Partnership	Active Mixing Membrane Oxygenator (P. Sawzik, PI)	Co-Inv undefined effort	3/96-2/97	35,000
NIH / HL54412	Integrated Blood Pump-Oxygenator for Neonatal Use – Phase I SBIR (K. Butler, PI)	Co-Inv 5% effort	9/95-7/96	100,000
UPMC Functional Imaging Program	NMR Imaging Applied to Improve Blood Oxygenator Design	P.I.	7/95-6/96	6,118
Medchem Corp.	1. Evaluation of Surgical Hemostatic Agents 2. Investigation of Variations in Activity Within Batches of Surgical Hemostatic Agents	P.I.	7/95-6/96	29,955
Vira I. Heinz Medical Research Fellowship	The Use of Bioactive Hydrogels in Wound Healing	Supervisor	5/96-9/96	2,500
Surgimedics Corp.	Analysis of Membrane Occlusion in an Autotransfusion Device	P.I. 10% effort	7/93-6/95	57,000
Competitive Medical Research Fund, Presbyterian Univ. Hospital	Graft Associated Thrombin in Left Ventricular Assist Device Patients	P.I. 15% effort	7/92-6/93	20,000
Medtronic Corp.	The Use of Heparin-Coated Cardiopulmonary Bypass Systems for: 1)Repair of Descending and Thoracoabdominal Aortic Aneurysms, and 2) Coronary Artery Bypass Grafting. Effects on Contact Activation of Blood Elements and Perioperative Blood Loss (G. Marrone, PI)	Co-Inv	7/91-6/92	13,000

Seminars and Invited Lectureships:

1. "Mechanisms of thrombus growth: the role of thrombin", Chemical and Petroleum Engineering Departmental Seminar, University of Pittsburgh, Pittsburgh, PA, October 1990.

2. "Biochemical mechanisms of mural thrombosis", Biochemical Engineering Department Seminar, University of California, Irvine, February 1991.

3. "Hematologic alterations associated with Novacor LVAD placement", Transplantation Seminar Series, University of Pittsburgh, September 1991.

4. "Thrombosis, biomaterials, and biocompatibility", Bioengineering Seminar Series, University of Pittsburgh, October 1991.

5. Discussant regarding "Artificial microvascular graft (AMG) failure: the role of GPIb", Dascombe WH, et al, and "Artificial micrograft failure in the baboon: roles of GPIIb/IIIa and thrombin", Garrett KO, et al, American College of Surgeons, Southwestern PA Chapter, Resident's Research Day, November 1991.

6. Discussant regarding "The effect of fibrin glue and batroxobin glue on platelet deposition and fibrinopeptide A generation after perfusion through human placental arteries", Dascombe WH, American College of Surgeons, Southwestern PA Chapter, Resident's Research Day, November 1992.

7. "Reperfusion after CPB: hematologic and coagulation alterations", Cardiovascular Research Conference, University of Pittsburgh, March 1993.

8. "Computational fluid dynamics and quantitative image analysis applied to thrombotic deposition in a membrane oxygenator", Medtronic Cardiopulmonary Division, Anaheim, CA, April 1994.

9. "The potential application of transcranial doppler imaging in assessing the biocompatibility of cardiopulmonary bypass circuitry", Medtronic Cardiopulmonary Division, Anaheim, CA, April 1994.

10. "Clinical modeling to determine the role of fibrinogen in vascular thrombosis", Scanning Microscopy International: Cells and Materials Conference, Toronto, Canada, May 1994.

11. "Membrane oxygenator design with computational techniques", Sarns / 3M Healthcare, Ann Arbor, MI, April 1995.

12. "Hematologic response to ventricular assist device implantation", Strategies to Improve Biocompatibility of Blood-Interacting Biomaterials, IBC Conference, Boston, MA, June 1995.

13. "Bioengineering: career options and current research", Governor's School of the Health Sciences, University of Pittsburgh, Pittsburgh, PA, August 1995.

14. "Cardiovascular device design: from clinical assessment to design optimization", Carnegie-Mellon University Biomedical Engineering Society Seminar, Pittsburgh, PA, November 1995.

15. "Artificial heart biocompatibility research", Orthopaedic Seminar Series, University of Pittsburgh Medical Center, Pittsburgh, PA, April 1996.

16. "Creating molecular barriers to thrombosis", Bioengineering Seminar Series, University of Pittsburgh, Pittsburgh, PA, February 1997.

17. "Forming molecular barriers on tissues", Pennsylvania Biotechnology Association 6th Annual Symposium, Philadelphia, PA, April 1997

18. "Directions in cardiovascular tissue engineering", Pittsburgh Tissue Engineering Initiative Retreat, Nemacolin Woodlands, PA, August 1997.

19. "Preventing cell/tissue adhesion with molecular barriers", Bioengineering Seminar Series, Rice University, Houston, TX, January 1998.

20. "Platelet activation in depression and ischemic heart disease", Forest Laboratories, New York, NY, May 1998.

21. "Assessing thrombosis and thromboembolism associated with cardiovascular devices", Stent Grafts: An Interdisciplinary Workshop, FDA Center for Veterinary Medicine, Laurel, MD, October 1998.

22. "Creating molecular barriers of polyethylene glycol to block cell adhesion onto tissue surfaces", Shearwater Polymers Inc., Huntsville, AL, December 1998.

23. "Thrombosis and thromboembolism in Novacor ventricular assist devices: the Pittsburgh experience", Novacor Protocol Meeting, Chicago, IL, January 1999.

24. "The basics of blood/material interactions", Cardiothoracic Resident Education Seminar, University of Pittsburgh, Pittsburgh, PA, June 1999.

25. "Assessing and addressing cardiovascular device biocompatibility", Gordon Conference on Biomaterials: Biocompatibility and Tissue Engineering, Holderness School, Plymouth, NH, July 1999.

26. "Evaluation of thromboembolism and hemostatic alterations in ventricular assist device patients", Devices and Diagnostics in Contact with Blood: Issues in Blood Compatibility at the Close of the 20th Century, Seattle, WA, August 1999.

27. "Applying flow cytometric techniques for the pre-clinical evaluation of blood pump biocompatibility", Devices and Diagnostics in Contact with Blood: Issues in Blood Compatibility at the Close of the 20th Century, Seattle, WA, August 1999.

28. "Where are we in rationally defining and testing blood compatibility, and using blood compatible materials in devices and diagnostics?", Panel Discussant, Devices and Diagnostics in Contact with Blood: Issues in Blood Compatibility at the Close of the 20th Century, Seattle, WA, August 1999.

29. "Cardiovascular device design and evaluation: working in Virchow's triad", Graduate Seminar in Department of Chemical, Bio, and Materials Engineering, Arizona State University, Tempe, AZ, September 1999.

30. "Flow cytometric assays to quantify platelet activation, aggregation, and life span in ventricular assist device implanted calves", Surfaces in Biomaterials Symposium, Scottsdale, AZ, September 1999.

31. "Targets for research in chronic support: thromboembolism", International Society for Heart and Lung Transplantation, Mechanical Cardiac Support and Replacement Symposium, Atlanta, GA, November 1999.

32. "Cardiovascular tissue engineering", Cardiothoracic Resident Education Seminar, University of Pittsburgh, Pittsburgh, PA, January 2000.

33. "Biocompatibility in ventricular assist devices present and future", Carnegie Mellon University Biomedical Engineering Program, Pittsburgh, PA, February 2000.

34. "Tissue engineered conduits for myocardial revascularization", Mini-Course in Advances in Myocardial Revascularization, General Surgery Grand Rounds, University of Pittsburgh, Pittsburgh, PA, March 2000.

35. "Biomaterials Education", Panel Discussant, 6th World Biomaterials Congress, Waikoloa, HI, May 2000.

36. "Thrombosis and thromboembolism in ventricular assist devices: blood, surface, and flow", Department of Mechanical Engineering, University of California at Santa Barbara, Santa Barbara, CA, December 2000.

37. "Engineering the cell adhesion response on damaged vascular tissues", Engineering Tissue Growth International Conference and Exposition, Pittsburgh, PA, March 2001.

38. "Tissue engineering: Regenerative medicine for people and economies", Eastern Mediterranean Chemical Engineering Conference, Ankara, Turkey, May 2001.

39. "Biocompatibility challenges in cardiovascular devices and the need for biological interfaces", Annual Meeting, Biomedical Engineering Society, Durham, NC, October 2001.

40. "Tissue engineering as a focus for economic development", Business Opportunities in Turkey, Appalachian-Turkish Trade Project, Pittsburgh, PA, March 2002.

41. "Biodegradable elastomers for use in soft tissue engineering", Engineering Tissue Growth International Conference and Exposition, Pittsburgh, PA, March 2002.

42. "Molecular barriers to cellular adhesion on tissue surfaces", University of Washington Engineered Biomaterials (UWEB) Summer Symposium on Non-Fouling Surfaces, Seattle, WA, August 2002.

43. "Biodegradable scaffolds for cardiovascular tissue engineering", Science2002: Synergy in Science, Pittsburgh, PA, September 2002.

44. "Engineering of vascular surfaces for targeted drug delivery and inhibition of clotting", World's Best Technologies 2002 International Conference, Pittsburgh, PA, September 2002.

45. "Synthetic scaffolds for cardiovascular tissue engineering", Pittsburgh Development Center Seminar Series, Magee-Women's Hospital, Pittsburgh, PA, September 2002.

46. "Nanotechnology in tissue engineering and drug delivery", Pennsylvania Nanotechnology 2002, Pennsylvania Nanotechnology Initiative, Harrisburg, PA, October 2002.

47. "Synthesis and characterization of highly elastomeric, bioerodible poly(ester-urethane)ureas for tissue engineering applications", Polymers in Medicine and Biology, American Chemical Society, Division of Polymer Chemistry, Rohnert Park, CA, November 2002.

48. "Processing nanofibers for tissue engineering applications", NanoScience and Engineering Conference, Pittsburgh, PA, December 2002.

49. "Flexible, biodegradable scaffolds for cardiovascular tissue engineering", Becton-Dickinson, Raleigh, NC, February 2003

50. "Flexible, biodegradable scaffolds for soft tissue engineering", University of Alabama at Birmingham, Dept. of Biomedical Engineering, Birmingham, AL, February 2003

51. "Processing of elastomeric scaffolds for cardiovascular tissue engineering", Engineering Tissue Growth International Conference and Exposition, Pittsburgh, PA, March 2003.

52. "Molecular barriers to cellular deposition. Molecular targets for drug delivery", Institute for Surgical Research, Fort Sam Houston, TX, April 2003.

53. "Materials for cardiovascular tissue engineering", McGowan Institute for Regenerative Medicine, Biomaterials Seminar Series, Pittsburgh, PA, May 2003.

54. "Stem cells: separating the hype from the hope", Pitt Alumni Club of Chicago, Chicago, IL, May 2003.

55. "Polyethylene glycol as a barrier to vascular thrombosis and target for vascular delivery", Boston Scientific, Natick, MA, June 2003.

56. "Materials for cardiovascular tissue engineering", McGowan Institute Cellular Approaches to Tissue Engineering and Regeneration Seminar Series, Pittsburgh, PA, September 2003.

57. "Soft tissue engineering with biodegradable elastomers", American Chemical Society Central Regional Meeting, Pittsburgh, PA, October 2003.

58. "Flexible, biodegradable scaffolds for cardiovascular tissue engineering", University of Arizona, Bioengineering Program, Tucson, AZ, November 2003.

59. "Reconstruction of the right ventricular outflow tract with a novel, biodegradable elastomer", 8th Annual Hilton Head Workshop, Cardiovascular Tissue Engineering: From Basic Biology to Cell-Based Therapies, Hilton Head, GA, March 2004.

60. "Designing scaffolds for mechanically demanding soft tissue applications", University of Michigan, Oral Health Sciences Program, School of Dentistry, Ann Arbor, MI, April 2004.

61. "Biomaterials", University of Pittsburgh, Materials Science Retreat, Pittsburgh, PA, May 2004.

62. "Thermoplastic elastomer design and processing for scaffold applications", Regenerate: Tissue Engineering the Human Body, Seattle, WA, June 2004.

63. "Cardiovascular organ engineering", National Institutes of Health, Bioengineering Research Partnership Grantee Meeting, Bethesda, MD, July 2004.

64. "Scaffold design for soft tissue", Transoma Medical Inc., Arden Hills, MN, August 2004.

65. "Building bioactivity into elastomeric scaffolds for cardiovascular tissue engineering", Bioengineered Blood Vessels and Valves 2004: Grafts, Stents, Valves and Tissue Engineering, UWEB 8th Annual Summer Symposium, University of Washington, Seattle, WA, August 2004.

66. "Trying to mend a broken heart: thermoplastic elastomers as scaffolding for cardiovascular engineering", University of Pittsburgh, Department of Materials Science and Engineering Seminar Series, Pittsburgh, PA, September 2004.

67. "In vivo surface modification of vascular tissue: interrupting thrombosis and targeting drug delivery", Genzyme Inc. visit to University of Pittsburgh, Pittsburgh, PA, December 2004.

68. "An overview of regenerative medicine and tissue engineering research in the Greater Pittsburgh region", Pittsburgh Life Sciences Greenhouse Press Tour, Pittsburgh, PA, January 2005.

69. "How do you mend a broken heart? Thermoplastic elastomers for cardiovascular tissue engineering", University of Illinois, Bioengineering Department, Urbana, IL, February 2005.

70. "Nanoscience and regenerative medicine", Biomedical Nanoscience, Integrated Research Team, US Army Medical Research and Materiel Command's Telemedicine and Advanced Technology Research Center, Frederick, MD, February 2005.

71. "Developing thermoplastic elastomers as a tool for cardiac repair", University of Wisconsin, School of Pharmacy Seminar Series, Madison, WI, April 2005.

72. "Biodegradable polymers for soft tissue engineering", International Workshop on Regenerative Medicine, Istituto Mediterraneo per i Trapianti e ad Alta Specializzazione, Palermo, Italy, April 2005.

73. "Thermoplastic elastomers as a tool for cardiovascular repair", University of Toronto, Institute of Biomaterials and Biomedical Engineering, Toronto, ON, April 2005.

74. "Processing thermoplastic elastomers for soft tissue engineering applications", Polymers in Medicine and Biology, American Chemical Society, Division of Polymer Chemistry, Rohnert Park, CA, June 2005.

75. "Biocompatibility considerations in mechanical circulatory support", Pediatric Circulatory Support Contractors Meeting, Bethesda, MD, June 2005.

76. "Molecular biocompatibility", American Society for Artificial Internal Organs Annual Conference, Washington, DC, June 2005.

77. "Using molecular design and polymer processing to create soft tissue engineering scaffolds", Wake Forest University, Institute for Regenerative Medicine, Winston-Salem, NC, July 2005.

78. Discussion Leader: "Materials-dependent in situ tissue regeneration", Gordon Conference on Biomaterials: Biocompatibility and Tissue Engineering, Holderness School, Plymouth, NH, August 2005.

79. "The blood-device interface", Gordon Conference on Assisted Circulation, Big Sky Resort, Big Sky, MT, August 2005.

80. "Nanomedicine and regenerative medicine", SciTech Spectacular, Carnegie Science Center, Pittsburgh, PA, October 2005.

81. "Directing molecular design and polymer processing toward soft tissue engineering", Medrad Corp., Indianola, PA, March 2006.

82. "Enter the world of regenerative medicine: Career options for engineers", National Society for Black Engineers 32nd Annual Convention, Pittsburgh, PA, April 2006.

83. "Developing thermoplastic elastomers for the engineering of soft tissue", Second International Conference on Epithelial Technologies and Tissue Engineering, Washington, DC, April, 2006.

84. "Scaffolding for cardiovascular tissues: Molecular design and processing", Center for Stem Cell and Regenerative Medicine, Case Western Reserve University and The Cleveland Clinic Foundation, Cleveland, OH, May, 2006.

85. Biocompatibility challenges in the design of a pediatric ventricular assist device", Biomedical Engineering Society Annual Meeting, Chicago, IL, October, 2006.

86. "Designing materials and constructing tissues for the cardiovascular system", Bioengineering Seminar Series, Center for Biomolecular and Tissue Engineering, Duke University, Durham, NC, November, 2006.

87. "Cardiovascular regenerative medicine: Designing material solutions", School of Materials & Chemistry, Zhejiang University, China, November, 2006.

88. "Synthesis and processing of biodegradable thermoplastic elastomers for soft tissue engineering", Materials Research Society Fall Meeting, Boston, MA, November, 2006.

Patents:

U.S. Patent #5,977,252 "Covalent Modification of Surfaces with Polymers to Increase Biocompatibility", filed 3/1996, notice of allowance 4/1998, issued 11/1999; assignee: University of Pittsburgh.

U.S. Patent #5,990,193 "Polymers for Reversible Photoinduced Sol Gel Transitions", filed 12/1995, issued 11/1999; assignee: University of Pittsburgh

U.S. Patent #6,174,645 "Polymer for Reversible Photoinduced Sol Gel Transitions", filed 5/1999, issued 1/2001; assignee: University of Pittsburgh

International Patent Application (#PCT/US97/03591) "Covalent Modification of Surfaceswith Polymers to Increase Biocompatibility", through University of Pittsburgh, filed 3/1997.

U.S. Patent Application (#60/059,399) "ICAM-1 Selective Antibody-Conjugated Echogenic Microbubbles", through University of Pittsburgh, filed 9/1997.

International Patent Application (#PCT/US98/19597) " ICAM-1 Selective Antibody-Conjugated Echogenic Microbubbles ", through University of Pittsburgh, filed 9/1998.

U.S. Provisional Patent Application (#60/214,865) "Localized delivery to a target surface", through University of Pittsburgh, filed 7/2000.

U.S. Patent Application (# 09/894,547) "Localized delivery to a target surface", through University of Pittsburgh, filed 6/01, pending with last action on 9/2005.

U.S. Provisional Patent Application (# 60/549,208) "Artificial alveolar-capillary modules for artificial lungs", through University of Pittsburgh, filed 3/2004.

U.S. Provisional Patent Application (# 60/805,980) "Biodegradable elastomeric patch for treating cardiac or cardiovascular conditions", through University of Pittsburgh, filed 6/2006.

Editorships:

1996-present	Editorial Board, *Journal of Biomedical Materials Research*
2002-present	Editorial Board, *Biotechnology & Bioengineering*
2006-present	Editorial Board, *Journal of Tissue Engineering and Regenerative Medicine*
2004-present	Founding Editor, *Acta Biomaterialia*

Journal Refereeing:

Annals of Biomedical Engineering
Annals of Thoracic Surgery
Artificial Organs
Biochimica et Biophysica Acta
Biological Psychiatry
Biomacromolecules
Biomaterials
Biotechnology Progress
Blood
Cells and Materials

Circulation
Colloids and Surfaces B: Biointerfaces
Gene Therapy
Journal of American Society for Artificial Internal Organs
Journal of the American College of Cardiology
Journal of Biomaterials Science, Polymer Edition
Journal of Biomedical Materials Research
Journal of Biomedical Materials Research: Applied Biomaterials
Journal of Laboratory and Clinical Medicine
Journal of Psychiatric Research
Journal of Thoracic and Cardiovascular Surgery
Journal of Vascular Surgery
New England Journal of Medicine
Polymer Bulletin
Scripta Materialia
Tissue Engineering

Study Section Memberships & Grant Reviewing:

The Whitaker Foundation, Biomedical Engineering Research Grant Reviewer, (1994).

Pittsburgh Tissue Engineering Initiative, Seed Grant Panel Review (1997-1999).

NIH – Surgery & Bioengineering Study Section, *ad hoc* grant reviewer (1998, 2000).

National Science Foundation (NSF), Small Business Innovative Research Grant Review Panel Member, Biotechnology/Biochemical Engineering, (1999).

Gordon Research Conferences, New Conference Proposal Review (2000, 2001).

Chairman, Pittsburgh Tissue Engineering Initiative, Technology Development Fund Seed Grant Review Panel (2000-2003).

National Science Foundation (NSF) – Proposal Reviewer, Biotechnology (2001).

Katholieke Universiteit, Leuven, Belgium; Research Council Grant Reviewer (2001, 2002).

University of Oklahoma, Bioengineering Foundation Reviewer (2001).

National Science Foundation (NSF), Small Business Innovative Research Grant Review Panel Member, Biotechnology/Biochemical Engineering (2002).

Oak Ridge Associated Universities, Ralph E. Powe Junior Faculty Enhancement Awards – Reviewer (2003, 2004, 2005).

NIH, National Institute of Dental & Craniofacial Research, Special Emphasis Panel, Restoration of Orofacial Tissues: A Biomimetic/Tissue Engineering Approach. For RFA-DE-03-004 (4/2003).

NIH, National Institute of Biomedical Imaging and Bioengineering, Study Section to review R01 applications on Advanced Biomaterials RFA. ZRG1 SSS-M 55 (8/2003).

NIH, Center for Scientific Review Special Emphasis Panel: Physiology and Pathobiology of the Organ Systems. ZRG1 F10 (20) (10/2004).

United States – Israel Binational Science Foundation – ad hoc grant proposal review (2004).

Deutsche Forschungsgemeinschaft (DFG), Review Panel for Establishment of a National Research Center in Regenerative Medicine (2004-2005).

NIH, Center for Scientific Review Special Emphasis Panel: Cardiovascular System, Toxicology, MOSS. ZRG1 DIG-B (21L) (3/2005).

NIH, Center for Scientific Review Special Emphasis Panel: Physiology and Pathophysiology of Organ Systems. ZRG1 F10-H (20) (11/2005).

NIH, Center for Scientific Review Special Emphasis Panel: Bioengineering Research Partnerships. ZRG1 SBIB-N (50) (12/2005).

Health Research Board, Ireland, Reviewer for 2006 Research Project Grant Scheme (4/2006).

NIH, Center for Scientific Review Special Emphasis Panel. ZRG1 SBIB-D (90) (5/2006).

LIST of CURRENT RESEARCH INTERESTS:

The research interests of my group are in the area of cardiovascular engineering with projects that address medical device biocompatibility and design, tissue engineering, and imaging. The research group is comprised of graduate students in Bioengineering and Chemical Engineering as well as post-doctoral fellows with backgrounds in surgery, engineering, or polymer chemistry. Projects span from *in vitro* to clinical studies.

1) Medical Device Biocompatibility and Design

The blood biocompatibility of circulatory assist devices has been of continuous interest to my group since arriving at the University of Pittsburgh. This work has involved clinical studies to characterize the mechanisms of thrombosis and thromboembolism in patients being bridged to cardiac transplantation, and the development of tools to assess blood biocompatibility in pre-clinical testing of next generation devices. Current emphasis is on the development of pumps for the pediatric population and involves the development of assays for the neonatal ovine model,

the assessment of platelet activation by shear forces, and the evaluation of coatings for these small rotary blood pumps.

A second area of long-standing interest is the development of blood oxygenators. This research has grown out of early work characterizing the effectiveness of heparin-coated devices in the clinical setting. Our group has developed computational fluid dynamics models to study blood flow within oxygenators and related this to thrombotic deposition. We continue to examine relationships between flow and thrombosis in multiple types of blood contacting devices. Current work is also focused on two projects developing biohybrid lungs wherein gas transfer surfaces are endothelialized to putatively reduce anticoagulation requirements for chronic pulmonary support.

Our work in the area of blood biocompatibility has lead to investigations of numerous other devices besides blood pumps and oxygenators. Currently we are involved with projects to develop a membrane system to scavenge deleterious host antibodies from perfused blood and a system to preferentially adsorb pro-inflammatory cytokines from patients at risk for septic shock. Our focus is most commonly on assessing and modifying one or more arms within Virchow's triad: blood, surface and flow. Our expertise in assessing the status of the hemostatic system has also lead to collaborations with colleagues in Psychiatry and Cardiology to evaluate platelet activation in, for instance, depression and in response to various pharmaceutical agents.

2) Cardiovascular Tissue Engineering

Our interest in cardiovascular tissue engineering grew from the observation that much of the early work in this field relied upon scaffold material such as poly(lactic-co-glycolic acid), which does not mechanically mimic the soft tissue properties characteristic of blood vessels and the heart. We have focused on the molecular design of thermoplastic elastomers that would be amenable to control at both the synthetic and processing stages to achieve scaffolds optimized for a given application. Our work to date has focused on applying these materials to the cardiac wall, as a reconstructive material and as a post-infarct patch, and as a small diameter blood vessel scaffold. We are also beginning to apply these materials as reconstructive fascia materials for traumatic injuries seen in the military arena.

3) Targeted Vascular Imaging

Since 1996 we have been involved in a close and productive collaboration with Dr. Flordeliza Villanueva of the Division of Cardiology at the University of Pittsburgh in the area of targeted vascular imaging. Our focus is currently on the development and characterization of ultrasound contrast media to illuminate regions of the microvasculature that are inflammatory or that are in a receptive state for angiogenesis. In the former case we have utilized models for cardiac transplant rejection and are ultimately interested in the non-invasive imaging of early markers of atherosclerosis. In the case of angiogenesis, we are interested in imaging tissue beds that would be responsive to growth factor (e.g. VEGF) therapy, as well as vasculature associated with growing tumors.

SERVICE:

Intramural Activities:

School of Medicine and University-wide:

1993-2001	Faculty Supervisor, Summer Medical Student Research Program
1993-present	Member Graduate Faculty
1995-	*Ad hoc* grant reviewer: University of Pittsburgh Medical Development Fund (also in 1997, 2004)
1995-present	Director of Thrombosis Research, Artificial Heart and Lung Program
1997-present	Reviewer: University of Pittsburgh Technology Transfer Office
1997-present	Consultant, Mental Health Clinical Research Center for Late-Life Mood Disorders, Western Psychiatric Institute and Clinic
1998-2001	Member, Operating Committee, McGowan Center for Artificial Organ Development
1998-2001	Member, Education Committee of the Division of Cardiothoracic Surgery
1999	Member, Clinical Research Curriculum Award (K30) Committee, School of Medicine
1999-2005	Commonwealth of Pennsylvania, Legislative Briefing Visits (1-2 per year) on McGowan Center for Artificial Organs and McGowan Institute for Regenerative Medicine (as Team Member and Leader), Harrisburg, PA
2000-2001	Director, Biohybrid Organ Development Program, McGowan Center for Artificial Organs
2001-present	Deputy Director and Executive Committee Member, McGowan Institute for Regenerative Medicine
2003-2004	Chairman, Research Oversight Committee (for conflict of interest review)
2003-present	Executive Committee, NIH Training Grant (T32), "Cellular Approaches to Tissue Engineering and Regeneration"
2003-present	Operating Committee, McGowan Institute for Regenerative Medicine

School of Engineering:

1993-1998	Ph.D. Qualifying Exam Committees, Chemical Engineering Department
1993-present	Ph.D. Qualifying Exam Committee Member, (2002-present as Committee Chairman), Bioengineering Department
1994-2004	Training Faculty, NSF Research Experience for Undergraduates, Chemical Engineering Department
1994-2001	Speaker and tour guide, undergraduate recruitment weekends and local high school engineering seminars
1994-1998	Training Faculty, NIH Biotechnology Training Grant
1995-1999	Training Faculty, Whitaker Special Opportunity Award for Program Enhancement in Bioengineering: Clinical Cardiovascular Bioengineering
1996-2005	Faculty Advisor, Biomedical Engineering Society (BMES) Student Chapter
1997-2005	Head of Curriculum Committee and Undergraduate Advisor for Biotechnology & Artificial Organs Track, Bioengineering Department
1997-2005	Faculty Search Committee, (for each search in this period), Bioengineering Department
1999	Member, Engineering School Thermodynamics Committee
1999-2000	Faculty Advisor, Bioengineering Senior Design Project
2003-present	Training Faculty, NIH Training Grant (T32), "Biotechnology Training Program"
2003-present	Member, Graduate Committee, Bioengineering Department
2003-present	Head of Graduate Track Committee in "Cellular and Organ Engineering", Bioengineering Department
2005-present	Executive Committee, NIH Training Grant (T32), "Cardiovascular Bioengineering"

Extramural Activities:

Industrial Consultantships:

Cardiac Assist Technologies
Medtronic
Sarns-3M
Medchem Products
Metamorphics
Cohesion
Vascor
Automated Cell Technologies
Compact Membrane Systems
Datascope Corp
Renal Solutions
Transoma
Genzyme
Ventracor

Conference Organization

Program Committee, American Society for Artificial Internal Organs (1995)

Program Committee, Society for Biomaterials (1995)

Organizer, Cardiovascular Tissue Engineering Section, Pittsburgh Tissue Engineering Initiative Retreat (1997)

Program Chairman for the Cardiovascular Biomaterials Special Interest Group of the Society for Biomaterials (1997-2000).

Vice-Chairman, Gordon Conference on Biomaterials: Biocompatibility and Tissue Engineering (2001)

Program Chairman for the Cell and Organ Therapy Special Interest Group of the Society for Biomaterials (2001-2002)

Scientific Advisory Committee, Regenerate – Tissue Engineering the Human Body, International Conference and Exhibition (2004)

Chairman, Gordon Conference on Biomaterials: Biocompatibility and Tissue Engineering (2003)

Program Committee, Society for Biomaterials, 2006 Annual Meeting

Program Committee, American Society for Artificial Internal Organs, 2006 Annual Meeting

Chairman, Tissue Engineering and Regenerative Medicine International Society, First World Congress, 2006

Bioengineering Track Chairman, ASAIO 53rd Annual Conference, 2007.

Session Organization and Chairmanship

1994	Session Chairman, "Cardiovascular", Society for Biomaterials Annual Meeting
1995	Session Chairman, American Society for Artificial Internal Organs Annual Meeting
1995	Session Chairman, "Cardiovascular Biomaterials", Society for Biomaterials Annual Meeting
1995	Session Organizer and Chairman, "Cardiovascular Biomaterials", Biomedical Engineering Society Annual Meeting
1996	Session Chairman, "Biomechanics and Biorheology", American Institute of Chemical Engineers
1996	Session Chairman, "Cardiovascular Biomaterials", 5th World Biomaterials Congress
1997	Session Chairman, "Blood Compatibility and Biodegradation", Society for Biomaterials Annual Meeting
1998	Co-Chair and Organizer, "Cardiovascular Stents: Materials, Thrombosis, and Restenosis", Workshop at the 1998 Society for Biomaterials Annual Meeting
1998	Session Chairman, "Biomedical Membranes", North American Membrane Society Annual Meeting- Biomedical Membranes
1998	Session Chairman, "In Vitro and In Vivo Blood Compatibility", Society for Biomaterials Annual Meeting
1999	Session Organizer and Chair for first jointly sponsored session by Society for Biomaterials and American Society for Artificial Internal Organs at Annual ASAIO meeting, "Smart Biomaterials and Biohybrid Organ Development"
1999	Session Chairman, "Blood Compatibility of Cardiovascular Biomaterials", Society for Biomaterials Annual Meeting
2000	Session Chairman, "Cardiovascular Biomaterials: Vascular Graft Surfaces", 6th World Biomaterials Congress
2000	Session Chairman, American Society for Artificial Internal Organs Annual Meeting
2000	Session Chairman, "Cellular Therapies", American Institute of Chemical Engineers Annual Meeting
2001	Session Chairman, "Healthcare II: Tissue Engineering", Eastern Mediterranean Chemical Engineering Conference
2002	Symposium Chairman, "Biomaterials for Cardiac Assist Devices", Society for Biomaterials Annual Meeting

2002	Session Chairman, "Biohybrid & Visceral Organs", Engineering Tissue Growth International Conference
2002	Symposium Organizer and Chairman, "Stem Cell Based Therapies", Society for Biomaterials Annual Meeting
2003	Session Chairman, "Scaffolds for Tissue Engineering", Society for Biomaterials Annual Meeting
2003	Session Chairman, "Scaffolds and Biomaterials", Engineering Tissue Growth International Conference
2004	Session Chairman, "Tissue Engineering II: Novel Scaffolds for Tissue Engineering", Biomedical Engineering Society Annual Meeting (co-sponsored with the Society for Biomaterials)
2004	Session Chairman, "Scaffolds, Gels and Encapsulants", Regenerate: Tissue Engineering the Human Body Conference
2004	Session Organizer and Chairman, "Bridging of Materials with Cells, Tissues and Organelles", American Society for Artificial Internal Organs
2005	Moderator, Poster Session "Bioengineering: Tissue Engineering and Regenerative Medicine", American Society for Artificial Internal Organs
2006	Moderator, Poster Session "Bioengineering", American Society for Artificial Internal Organs

Professional Society Service (Other Than Meeting-Related):

2000-2004	American Society for Artificial Internal Organs, Membership Committee
2002-2003	Tissue Engineering Society of North America – Steering Committee
2005	Poster Award Review Committee, Tissue Engineering & Biomaterials Track, Biomedical Engineering Society
2005	American Institute for Medical and Biological Engineering, Finance Committee
2005-present	Member, Continental Council, Tissue Engineering and Regenerative Medicine International Society (TERMIS)

Other Extramural Activities:

1992-present	Faculty Supervisor, Undergraduate Biomedical Engineering Research Program, Carnegie-Mellon University

2000-2001	International Technology Research Institute (ITRI), World Technology (WTEC) Division: evaluation of worldwide expertise in tissue engineering, panel member for evaluation of Europe (sponsored by NSF, NIH, FDA, DARPA, NIST, NASA)
2000-2003	Chairman of Pittsburgh Tissue Engineering Initiative Technology Development Fund Seed Grant Review Panel
2001	WQED Pittsburgh (local PBS affiliate) – Science and Nature Programming Consultant
2004-2006	South Carolina Bioengineering Center for Regenerative Medicine, Clemson University and Medical University of South Carolina Center of Biomedical Research Excellence (NIH-COBRE), advisory committee
2005	Bioengineering Textbook Reviewer – Elsevier
2005	Acadèmic Program Review Committee for the University of Arizona Graduate Interdisciplinary Program in Biomedical Engineering
2006	University of Pittsburgh representative for the Roundtable on Biomedical Engineering Materials and Applications (BEMA), sponsored by the National Research Council, Institute of Medicine, and National Academy of Engineering

In Vivo PEG-Modification of Vascular Surfaces for Targeted Delivery

Timothy E. Deglau, MSE,[a,b], Flordeliza S. Villanueva, MD,[b,c,d], and William R. Wagner, PhD,[a,b,c,e] *Pittsburgh, PA*

[a] Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA
[b] McGowan Institute for Regenerative Medicine (MIRM), University of Pittsburgh, Pittsburgh, PA
[c] Department of Surgery, University of Pittsburgh, Pittsburgh, PA
[d] UPMC Cardiovascular Institute, Pittsburgh, PA
[e] Department of Chemical Engineering, University of Pittsburgh, Pittsburgh, PA

Corresponding Author: William R. Wagner
100 Technology Drive
Bridgeside Point Building (Rm. #226)
Pittsburgh, PA 15219
Telephone: (412) 235-5138
Fax: (412) 235-5110
Email: wagnerwr@upmc.edu

ABSTRACT

Objective: Thrombosis and restenosis are common problems associated with intravascular procedures. Previously, we demonstrated that modifying the injured vascular surface with a protein-reactive polymer could block undesirable platelet deposition. As an added benefit, it would be advantageous if one could target therapeutics to the injured site. This study investigates a site-specific delivery system to target microspheres to vascular surfaces modified with a reactive polyethylene glycol tagged with biotin.

Methods: Rabbit femoral arteries were injured with a 2F embolectomy catheter. Modification of the injured surface was achieved using a channeled balloon catheter or small diameter tube. Microspheres were injected intravenously through catheterization of the ear vein. Polymer modification on the injured surface and delivery of microspheres was quantified using epi-fluorescence microscopy at 0, 24, 48, and 72 hrs.

Results: Maximum polymer coverage occurred at 0 hr with a mean intensity of 1,529 and decreased to 1,311 (24 hrs), 1,110 (48 hrs), and 1,028 (72 hrs) over time. The number of microspheres per mm^2 binding to modified, injured arteries was 304 versus 141 for the damaged, un-modified control at 0 hrs ($P < .01$). At subsequent times, the number of adherent microspheres/mm^2 decreased to 150 at 24 hrs ($P < .01$), 86 at 48 hrs ($P < .01$), and 50 at 72 hrs ($P < 0.025$). After 0 hr, the non-specific binding to injured, un-modified arteries decreased sharply to 10 microspheres per mm^2. Microspheres binding to modified, healthy arteries was 153 microspheres/mm^2 as opposed to 26 for the un-modified, healthy control at 0 hrs ($P = 0.005$).

Conclusions: Polymer modification of the vascular surface could be achieved using a channeled drug delivery catheter or small diameter tube with similar results. Using a fluorescent polymer,

modification of the balloon injured artery was verified with greater than 67% of the initial fluorescence remaining at 72 hrs. Targeted microspheres preferentially adhered to polymer-modified surfaces as opposed to injured, un-modified or healthy vascular surfaces.

Clinical Relevance: Results of intravascular procedures are often complicated by thrombosis and restenosis at the sites due to vascular injury. These results demonstrate the feasibility of providing site-specific recognition signals for delivery of agents to healthy and damaged vascular tissue, which could prove valuable in a variety of clinical settings where the localization of therapeutics is desirable. In particular, the delivery of anti-mitotic or anti-thrombotic pharmaceuticals to arterial lumens following angioplasty or endarterectomy or chemotherapeutic agents to tumor vasculature might be feasible.

INTRODUCTION

Heart and cerebrovascular diseases are two of the leading causes of mortality in the United States accounting for approximately 37% of all recorded deaths.[1,2] Coronary artery disease and carotid stenoses are primarily caused by atherosclerosis within blood vessels. Atherosclerosis is triggered by multiple factors such as endothelial dysfunction or injury, vascular smooth muscle cell proliferation, inflammation, and alterations in the extracellular matrix.[3] Percutaneous transluminal coronary angioplasty is now the most common treatment for patients with coronary artery disease. Carotid stenoses are primarily alleviated through surgical procedures know as carotid endarterectomies; however, carotid angioplasty is gaining popularity. Unfortunately, long-term success of angioplasty and stenting procedures has been limited by re-narrowing of the vessels known as restenosis.

Many factors contribute to restenosis following intravascular procedures. Disruption of the endothelial layer and exposure of a thrombogenic surface leads to platelet and leukocyte deposition immediately following the angioplasty procedure leading to thrombus formation and inflammation.[4] In addition, balloon inflation also leads to dissections within the arterial wall causing injury to the smooth muscle cells.[5,6] Factors released by platelet and leukocytes as well as direct injury of the cells causes smooth muscle cells to proliferate, migrate, and deposit more extracellular matrix resulting in neointimal hyperplasia.[5,6] Over time, the thrombogenic and inflammatory surface, disruption of the endothelial layer, and intimal hyperplasia lead to restenosis within the vessel and the need for additional follow-up therapies.

In the current study, a protein-reactive polymer is employed to modify injured vascular surfaces in the hopes of blocking thrombosis and providing a site for the targeted delivery of therapeutics as a means of preventing restenosis. N-hydroxysuccinimide-polyethylene glycol (NHS-PEG) is used to covalently modify vascular surfaces in an in vivo rabbit femoral artery model of vascular injury. The NHS reactive group covalently links with primary amines, with the most accessible being the epsilon amine of found on the amino acid lysine.[7] A stable amide bond is formed covalently linking the protein-reactive polymer with a primary amine of a protein on a vascular surface.[8,9] Previous research demonstrated that modification of vascular surfaces with a protein-reactive PEG forms a molecular barrier preventing platelet and leukocyte adhesion.[10,11]

In addition to blocking thrombosis at sites of vascular injury, it would be advantageous to have a means of targeting intravenously injected agents to labeled vascular segments for further therapeutic benefit. This could be accomplished by addition of biotin to the terminus of the reactive PEG. N-hydroxysuccinimide-polyethylene glycol-biotin (NHS-PEG-biotin) could

modify vascular tissue and provide a site for the targeted delivery of agents relying upon the high affinity between biotin and avidin ($K_a = 10^{15}$ M^{-1}).[7] Targeting systems exploiting the strong interaction between biotin and avidin have previously been explored as possible treatment modalities for tumors and whole organs.[12,13] For our current system under investigation, we chose to use a deglycosylated form of avidin with similar binding characteristics and lower non-specific binding known as NeutrAvidin. NeutrAvidin-coated microspheres were chosen as a model to evaluate the feasibility of targeting particulate drugs, liposomes, or vesicles to PEG-biotin modified vascular segments. As proposed, modifying vascular surfaces with the protein-reactive PEG-biotin should inhibit platelet deposition as well as provide a target for the site-specific delivery of microspheres for intravascular treatments (Fig 1).

MATERIALS AND METHODS

Surgical Procedure

The animal studies were completed following a protocol approval by the Institutional Animal Care & Use Committee of the University of Pittsburgh. This study employed a rabbit femoral artery model to evaluate the proposed modification and targeting system.[10] Female New Zealand White rabbits (Myrtle's Rabbitry, Inc., Thompson Station, TN) with an average weight of 4.25 kg were anesthetized with an intramuscular injection of 40 mg/kg ketamine (Webster Veterinary, Sterling, MA) and 5 mg/kg xylazine (Webster Veterinary, Sterling, MA) and sustained on 1.5-2.5% isoflurane (Webster Veterinary, Sterling, MA) administered endotracheally. An ear vein of the rabbit was cannulated with a 22 G x 1 in JELCO IV catheter (Webster Veterinary, Sterling, MA) to provide intravenous access. Fluids were provided with a slow drip of Lactated Ringers (Webster Veterinary, Sterling, MA) through a Venoset Microdrip

IV set (Webster Veterinary, Sterling, MA). An incision was made in the skin exposing the underlying muscle. The muscle was carefully dissected exposing the common femoral, saphenous, and popliteal arteries. Minor side branches off the common femoral artery were ligated and removed. SUNDT Slim-Line aneurysm clips (Codman, Raynham, MA) were placed on the common femoral artery just proximal to the deep femoral artery branch and on the popliteal artery. An arteriotomy was made in the saphenous artery to allow access to the lumen of the common femoral artery. Only one leg was used in survival studies to minimize trauma to the animal and allow for adequate mobility for water and food intake. In acute studies, the same procedure was repeated on the other leg of the animal to minimize the number of animals required for statistically significant results.

Balloon Injury

A 2F Fogarty embolectomy catheter (Edwards Lifesciences, Irvine, CA) was inserted through the arteriotomy in the saphenous artery until it reached the clamp on the common femoral artery. The balloon was then inflated with air using a 1 mL BD slip-tip disposable tuberculin syringe (Fisher Scientific, Pittsburgh, PA) until the vessel distended slightly. Next, the inflated balloon was withdrawn from the vessel until it reached the branch where the popliteal and saphenous emerge from the common femoral artery. At this point, the balloon was deflated and the procedure repeated three times to ensure vascular injury.[14,15] Finally, the 2F Fogarty embolectomy catheter was left deflated after the third pass and removed from the arteries through the arteriotomy.

Denudation of the endothelial layer and vascular injury resulting from the passage of the embolectomy catheter was confirmed using Evans blue dye.[16] Evans blue is an azo dye that

binds with circulating albumin.[16] An intact endothelium would serve as a barrier to this protein-dye complex, but the complex adsorbs onto denuded arterial segments staining the surface a royal blue color.[16] Following arterial injury with a 2F Fogarty embolectomy catheter, a small group of rabbits were given an intravenous dose of 10 mg/kg Evans blue dye two hours prior to sacrifice.[16] The uninjured common femoral artery in the other leg was harvested as a control. Femoral arteries injured with the embolectomy catheter appeared blue while healthy vessels appeared white (data not shown).

Modification with PEG

Modification of the arteries was accomplished using either a .025 in outer diameter Micro-Renathane tubing (Braintree Scientific, Braintree, MA) or 2.5 mm Remedy channeled drug delivery balloon catheter (Boston Scientific, Natick, MA). The tube or drug delivery balloon catheter was introduced into the common femoral artery through the arteriotomy in the saphenous artery and threaded until the tip reached the clamp. An aliquot of Phosphate Buffered Saline (PBS) (Cambrex, Walkersville, MD) was added to a pre-weighed sample of NHS-PEG-biotin MW 3,400 or NHS-PEG-fluorescein MW 5,000 (Nektar Therapeutics, San Carlos, CA) to make 1 mL of a 10 mM solution. The solution was mixed until the solid dissolved and then loaded into a 1 mL BD slip-tip disposable tuberculin syringe. Next, the syringe was connected to the port on the drug delivery balloon catheter or to a 27 G x ½ in BD PrecisionGlide needle (Fisher Scientific, Pittsburgh, PA) inserted into the end of the tube to allow for addition of the polymer for modification of the vessel. The polymer was continuously flushed through the lumen of the vessel for a period of 45 s. After addition of the polymer, the tube or balloon catheter was withdrawn from the common femoral through the arteriotomy and a previously

placed ligature was tightened where the saphenous artery branches off the femoral artery. When the total incubation time for the polymer in the artery reached 1 min, the aneurysm clips were removed from the popliteal and common femoral arteries to restore blood flow through the femoral and remove any un-reacted polymer. Control arteries were treated in an identical manner except that the vehicle, PBS, was added instead of the reactive polymer.

In the case of modifying healthy vasculature, the tip of a 30 G x ½ in BD PrecisionGlide needle (Fisher Scientific, Pittsburgh, PA) was bent to make a curved 90° angle and inserted into the common femoral artery lumen near the clamp for injection of the polymer for vessel modification. Again, an aliquot of PBS was added to a pre-weighed sample of NHS-PEG-biotin to make 1 mL of a 10 mM solution. The solution was mixed until the solid dissolved and then loaded into a 1 mL BD slip-tip disposable tuberculin syringe. Next, the syringe was connected to the curved needle and inserted into the lumen of the common femoral artery just before the aneurysm clip with the bevel facing toward the saphenous and popliteal branches. The polymer was continuously flushed through the lumen of the vessel and out the site of the arteriotomy in the saphenous artery for a period of 45 s. After addition of the polymer, the needle was carefully withdrawn from the common femoral artery and a small amount of Avitene Flour, a microfibrillar collagen hemostat, (Davol, Inc., Cranston, RI) was placed at site of access to control bleeding. In addition, a previously placed ligature was tightened where the saphenous artery branches off the femoral artery. When the total incubation time for the polymer in the artery reached 1 min, the aneurysm clips were removed from the popliteal and common femoral arteries to restore blood flow through the femoral and remove any un-reacted polymer. Control arteries were treated in an identical manner except that the vehicle, PBS, was added instead of the reactive polymer.

Acute Studies

The open surgical site was covered with a 4 x 4 in Fisherbrand gauze sponge (Fisher Scientific, Pittsburgh, PA) saturated in 0.9% sodium chloride irrigation solution (Fisher Scientific, Pittsburgh, PA) to keep the site moist. For the PEG modification experiments, the vessels were harvested as per the protocol described in the Specimen Collection section. In the case of the acute microsphere targeting studies, the targeted microspheres were administered as illustrated in the Targeting of Microspheres section.

Survival Studies

For measurements collected at 24, 48, and 72 hrs, the surgical sites were closed and the animals recovered. 2-0 Ethicon coated Vicryl sutures with taper point needles were used to close the muscle and for subcutaneous closure of the skin. Once the wound was closed, the anesthesia was discontinued and the rabbits were monitored until they regained consciousness and returned to their housing. Rabbits were given intramuscular injections of 1 mg/kg ketoprofen (Webster Veterinary, Sterling, MA) and 100 mg cefazolin (Webster Veterinary, Sterling, MA) twice a day until final disposition of the animal.

Targeting of Microspheres

In the case of the 0 hr time point, intravenous access was already established at the beginning of the surgical procedure, which permitted administration of the microspheres. For the extended time points, the animals were anesthetized and an ear vein catheterized as described previously in the Surgical Procedure section. A bolus of 4.80×10^8 particles of yellow-green

fluorescent Fluospheres NeutrAvidin labeled microspheres (Molecular Probes, Eugene, OR) in 1 mL of PBS was loaded into a 1 mL BD slip-tip disposable tuberculin syringe. An 18 G x 1 ½ in BD PrecisionGlide needle (Fisher Scientific, Pittsburgh, PA) was placed on the tip of the syringe and the needle inserted into an access port on the Venoset Microdrip IV set. The entire solution of microspheres was injected into the rabbit over a period of 30 s and then flushed with Lactated Ringers solution. The microspheres were allowed to circulate in the bloodstream of the rabbit for 1 hr before the vessels were harvested.

Specimen Collection

Animals were maintained on 2.5% isoflurane. A midline incision was made from below the rib cage to the pelvic region. Next, the vena cava and aorta were isolated from the surrounding tissue. At this point, the isoflurane was increased to 5% and the animals euthanized with a supersaturated potassium chloride (KCl) solution (Sigma, St. Louis, MO). The aorta was cannulated with an 18 G x 1 in JELCO IV catheter (Webster Veterinary, Sterling, MA) and the hind limb portion of the animals was flushed with 100 mL of Lactated Ringers through a Venoset IV set (Webster Veterinary, Sterling, MA). The vena cava was severed to allow the excess blood and fluid to drain from the hind limb region. After the blood was flushed, 100 mL of Shandon Glyo-Fixx (Thermo Electron Corporation, Waltham, MA) was administered through a Venoset IV set to pressure fix the arteries for examination. Experimental and control femoral arteries were explanted from the rabbit after fixation along with some carotid arteries, which served as another control in some instances. The explanted vessels were placed in a labeled 6 well tissue culture plate (Fisher Scientific, Pittsburgh, PA) and transported back to the lab for processing. Excess tissue was removed from the exterior of the arteries and they were filleted

lengthwise to expose the lumen. Minutien pins (Fine Science Tools, Foster City, CA) were used to secure the edges of the vessel to pink dental wax (Electron Microscopy Sciences, Hatfield, PA) with the lumen side facing upwards. After securing the vessel to the wax, the sample was placed back into the 6 well tissue culture plate overnight before evaluation using epi-fluorescence microscopy.

Epi-Fluorescence Microscopy of Samples

A Zeiss Axiovert 35 Epi-Fluorescence Microscope (Carl Zeiss, Inc., Thornwood, NY) with a MicroMAX 5 MHz CCD Camera (Princeton Instruments, Trenton, NJ), Mac G4 computer (Apple, Cupertino, CA), and IP Lab (Scanalytics, Inc., Billerica, MA) were used to capture images from the vessels. In addition, the IP Lab software was utilized for measuring fluorescence intensity of the polymer in the modification experiments and quantifying the microsphere binding in targeting experiments. Micrographs of the explanted vessels were taken at 1 mm increments starting where the saphenous and popliteal arteries branched from the femoral and ending at the site of the clamp on the common femoral artery. The fluorescent polymer was labeled with fluorescein, which has a maximum absorption of 490 nm and emission of 514 nm. Using the same filter and exposure settings, the fluorescence intensity of the polymer was measured over the course of 72 hrs and the persistence of the polymer modification determined. The Fluospheres NeutrAvidin labeled microspheres were yellow-green fluorescent with excitation/emission spectra of 505 nm and 515 nm, respectively. IP Lab software was employed to quantify the number of adherent microspheres to polymer modified and control surfaces.

Statistical Analysis

Statistical analysis of the data acquired from the vessel images was performed using the Analysis Toolpak in Microsoft Excel. Data points are represented as mean values with either their standard deviation (St Dev) or standard error of the mean (SEM) as denoted in the figures and/or their legends. Differences between control and treated groups for PEG duration and microsphere targeting to balloon injured rabbit femoral arteries, at all time points, were evaluated using a two-factor ANOVA with replication to determine statistical significance. For microsphere targeting experiments to healthy endothelium, control versus treated group comparisons were made using a Student's *t*-test with $p < .05$ being considered statistically significant.

RESULTS

Modification Techniques

Modification of the balloon injured rabbit femoral arteries with NHS-PEG-fluorescein was evaluated using a .025 in outer diameter Micro-Renathane tube and 2.5 mm Remedy channeled drug delivery balloon catheter. The background auto-fluorescence was negligible (Fig 2, A). A similar pattern of modification was seen with both the Micro-Renathane tubing and the channeled drug delivery balloon catheter (Fig 2, B, C). This was further confirmed by measuring the fluorescence intensity of vessel segments modified with the polymer delivered using the Micro-Renathane tubing and Remedy channeled drug delivery balloon catheter. Modification of balloon injured arteries with NHS-PEG-fluorescein resulted in nearly identical fluorescence intensities with a mean of 1241 for the tube and 1230 for the channeled balloon catheter (Fig 3). Control vessels showed little to no auto-fluorescence with a mean fluorescence intensity of only

69 (Fig 3). There was no difference in modification of balloon injured arteries regardless of whether the Micro-Renathane tubing or Remedy drug delivery catheter were used for administration of the reactive PEG. Since there was no difference in the ability to deliver the polymer with either technique, subsequent experiments evaluating the duration of the polymer in the vessel or ability to target microspheres to the polymer were completed using the Micro-Renathane tubing. The Micro-Renathane tubing was selected because of its smaller size in comparison to the Remedy channeled drug delivery balloon catheter, which allowed for easier introduction into the rabbit saphenous artery with fewer complications.

PEG Duration

In order to assess the ability of the polymeric barrier to inhibit thrombosis and as a site for the targeted delivery of therapeutics, it was important to establish the maintenance of the polymer on the vascular surface post-modification. It was apparent that the polymer coverage decreased over time, but remained on balloon injured vessels for the entire evaluation period of 72 hrs (Fig 4). There was little to no background auto-fluorescence associated with control vessels at any time point with a mean fluorescence intensity of only 101 (Fig 4). The maximum coverage occurred at 0 hr with a mean intensity of 1,529, which then decreased gradually over the next 72 hrs (Fig 4). At 24 hrs, the mean fluorescence intensity dropped to 1,312 and then further decreased to 1,110 and 1,028 at 48 and 72 hrs, respectively (Fig 4). Even though the polymer remaining on the balloon injured vessel declined over time, greater than 67% of the original fluorescence was maintained at 72 hrs (Fig 4). As a result, the modification of the balloon injured arteries with the polymer would likely be maintained for even longer time than 72 hrs.

The ANOVA performed on the PEG duration data revealed that the mean fluorescence intensity varies with the treatment (control vs. NHS-PEG-fluorescein) as well as the time post-modification (0, 24, 48, and 72 hrs) with a significance value of $p << .001$ (Fig 4). In addition, the ANOVA demonstrated that there was interaction between the treatment and post-modification time with significance of $p << .001$ (Fig 4). The fluorescence intensity did not depend upon the post-modification time for the control vessels (Fig 4). However, the mean intensity of the NHS-PEG-fluorescein treated femoral arteries decreased as the time post-modification increased (Fig 4).

Along with evaluating the maintenance of the polymer, fluorescence intensity data from the images along the entire length of the balloon injured vessels modified with the fluorescent PEG were used to determine the consistency of the polymer coverage. The fluorescence intensity of the vessel segments remained fairly consistent over the entire length for the 0, 24, 48, and 72 hr time points (Fig 5). There was some fluctuation of the mean intensity of the fluorescent polymer over the length of the vessel, but the coverage remained fairly uniform (Fig 5). Establishing the consistency of the polymeric coverage along the entire length of the modified vessel was important in evaluating the effectiveness of the barrier to inhibit thrombosis or the signal to deliver targeted therapeutics.

Microsphere Targeting

NeutrAvidin-coated microspheres preferentially adhered to balloon injured arteries modified PEG-biotin as opposed to balloon injured, un-modified vascular surfaces at all time points evaluated (Fig 6). A total of 304 microspheres per mm^2 bound to PEG-biotin modified balloon injured femoral arteries as compared to 141 microspheres per mm^2 for the injured, un-

modified control at 0 hrs (Fig 6). Some non-specific binding of NeutrAvidin-coated microspheres to injured, un-modified femoral arteries was observed at 0 hrs (fig 6). The total number of adherent microspheres to PEG-biotin modified, balloon injured arteries decreased as the time post-modification increased (Fig 6). However, the ability to target NeutrAvidin-coated microspheres was maintained for a minimum of 72 hrs (Fig 6). At 24 hrs; the number of adherent microspheres to PEG-biotin modified, balloon injured arteries was 150 per mm^2 (Fig 6). This number further decreased to 86 at 48 hrs and 50 at 72hrs (Fig 6). In comparison, the non-specific binding of NeutrAvidin-coated microspheres diminished sharply to an average of 10 microspheres per mm^2 at all times greater than 0 hrs (Fig 6). This data confirmed that the NeutrAvidin-coated microspheres were preferentially targeted to PEG-biotin modified as opposed to control balloon injured rabbit femoral arteries. In addition, the ability to target microspheres to the polymer modified vascular surfaces was maintained for a minimum of 72 hrs.

The ANOVA performed on the microsphere targeting data revealed that the mean number of microspheres per mm^2 varied with the treatment (untreated vs. NHS-PEG-biotin) as well as the delivery time post-modification (0, 24, 48, and 72 hrs) with a significance value of $p << .001$ (Fig 6). In addition, the ANOVA demonstrated that there was interaction between the treatment and delivery time with a significance of $p << .001$ (Fig 6). The number of adherent microspheres per mm^2 decreased sharply from 0 to 24 hrs and then remained constant out to 72 hrs for untreated, balloon injured rabbit femoral arteries (Fig 6). Furthermore, the number of microspheres per mm^2 binding to the NHS-PEG-biotin treated femoral arteries decreased as the time before infusion of the microspheres increased (Figure 7-4).

In addition to targeting pharmaceuticals to sites of vascular injury, we evaluated the ability of using the same targeting strategy to target agents to healthy vascular tissue, which would be applicable for delivering chemotherapeutics to tumor vasculature. This application was evaluated by addition of the reactive polymer or vehicle control to uninjured rabbit femoral arteries as described in the Materials and Methods section. As was the case with targeting to balloon injured arteries, the NeutrAvidin-coated microspheres were preferentially targeted to healthy vascular tissue modified with the polymer as opposed to the un-modified arteries (Fig 7). A total of 153 microspheres per mm^2 bound to PEG-biotin modified healthy femoral arteries as opposed to only 26 microspheres per mm^2 for the un-modified control at 0 hrs ($P = .005$) (Fig 7). The total number of microspheres adhering to PEG-biotin modified healthy tissue at 0 hr (Fig 7) was less than that seen with the PEG-biotin modified, balloon injured arteries (Fig 6). However, the difference in targeting between the control and polymer modified vessel surfaces was greater for the healthy tissue (Fig 7) as opposed to the balloon injured femoral arteries (Fig 6) at 0 hrs.

DISCUSSION

Modifying vascular surfaces with a reactive PEG could serve various functions. The reactive PEG could be employed to form a molecular barrier on damaged vascular surfaces to inhibit platelet deposition.[10,17] In addition, vascular surfaces labeled with a reactive PEG could be utilized as a site-specific target to deliver agents to the modified locations. A tag, such as biotin, on one end of the PEG molecule could facilitate the capture of therapeutic agents conjugated to avidin or one of its derivatives. PEG-biotin modified surfaces could provide a target for the delivery of proteins, drugs, microspheres, or cells. It would be beneficial to deliver anti-mitotic or anti-inflammatory therapeutics to sites of vascular injury such as those found after

balloon angioplasty, carotid endarterectomies, and anastamoses. Furthermore, it might be possible to deliver chemotherapeutic agents to PEG-biotin modified tumor vasculature. The data presented in this paper demonstrate the ability of modifying healthy and injured vascular tissue with a protein-reactive polymer for site-specific delivery of microspheres in a clinical setting.

A number of studies have endeavored to block thrombosis and recurrent restenosis at the site of vascular injury using a number of different strategies. Coatings have been applied to injured vascular surfaces to physically inhibit platelet deposition. Another tactic is to use a hydrogel to prevent platelet deposition by creating a barrier and for sustained release of therapeutics. Furthermore, local intravascular drug or gene delivery has been employed to curb intimal hyperplasia. Drug-eluting stents are still yet another avenue aimed at preventing restenosis following angioplasty of stenosed vessels. Modification of vascular surfaces with a reactive PEG as described in this study is applicable to all of the current strategies under investigation.

Nanocoatings of hyaluron and chitosan deposited onto damaged vascular surfaces have been used to inhibit platelet deposition [18]. One of the drawbacks of the hyaluron and chitosan nanocoatings is that formation of a suitable barrier requires multiple administrations of the polyelectrolytes.[18] Another study focused on concealing extracellular matrix ligands with a PEGylated fibronectin, which interacts with fibrillar collagens, to reduce platelet recognition and binding.[19] However, this method of camouflaging ligands associated with platelet recognition and binding with PEGylated fibronectin required 30 min to cover the injured vascular surface.[19] Both the hyaluron and chitosan nanocoatings and PEGylated fibronectin systems for inhibiting intravascular thrombosis require extended application periods or repeated administrations, which may be detrimental in time-sensitive procedures. The protein-reactive PEG employed to in our

system rapidly modifies vascular surfaces (less than 1 min) with only a single application required. Modification of biomaterials with a protein-reactive PEG has been shown to reduce thrombosis on biomaterial surfaces.[11] Furthermore, the reactive PEG has demonstrated an ability to inhibit thrombosis on injured vascular surfacers.[10,17] The molecular barrier thickness could easily be controlled by changing the Molecular Weight (MW) or branching of the polymer molecule still applied in a single treatment.

Hydrogel barriers formed by photopolymerization have also demonstrated an ability to inhibit thrombosis and reduce intimal thickening on injured vascular surfaces.[20,21] The hydrogel establishes a barrier preventing blood from contacting the injured vessel wall, which would prevent platelet adhesion and thrombus formation.[20] Formation of the hydrogel barriers using photopolymerization requires additional steps such as adsorption of a photoinitiator on the injured vessel surface, flushing of excess initiator, administration of the hydrogel precursors, and adequate illumination (external or internal) to form the gel.[20,21] In our study, the protein reactive PEG can be applied to the vascular surface in one step while angioplasty is being performed at the site using a channeled drug delivery catheter. PEG hydrogels have also been synthesized to release nitric oxide (NO) or YC-1, a benzyl indazole derivative, as therapeutic agents to reduce platelet adhesion and smooth muscle cell proliferation after vascular injury.[22,23] Therapeutics such as these and others could be delivered to PEG-modified vascular sites using the targeting strategy under investigation in this paper.

Another method of inhibiting thrombosis and restenosis at sites of vascular injury involve local administration of drugs or gene therapy vectors to the injured vessels. Local delivery of drugs, gene therapy vectors, and vectors can be accomplished using specialized drug delivery catheters that employ passive, pressure-driven, electrically, or mechanically enhanced diffusion

for delivery.[24-26] The protein-reactive PEG investigated here would be delivered with one of these specialized drug delivery balloon catheters. However, the polymer coating should act as a barrier, preventing platelet deposition and thrombus formation, as well as providing a site for the targeted delivery of intravenously administered therapeutics over an extended times. Using the drug delivery catheters for direct delivery of the agents only allows for one application. Another approach used delivery of losatran from fibrin glue applied at the site of vascular injury to prevent restenosis.[27] The difficulties with using fibrin glue are that elution of the entrapped agent occurred very rapidly preventing long-term delivery and the technique cannot be used with angioplasty because it requires vessel access.[27]

Local delivery of therapeutics is also possible by targeting the molecules or using targeted carriers to direct the therapy to specific vascular segments. One such method targets heparin or low molecular weight heparin conjugated to antibodies against cross-linked heparin, which is deposited at the site of arterial injury, to reduce neointimal formation.[28] Another method targets microspheres or particles to selected vascular sites using antibodies to exposed surface markers. Hyaluron microspheres conjugated to antibodies against E- and P-selectin preferentially adhered to inflammatory vascular sites and successfully delivered plasmid DNA.[29] Similarly, biodegradable particles conjugated to antibodies for E- and P-selectin, ICAM-1, and VCAM-1 also showed targeting to inflamed endothelium.[30] Unlike the methods described here, our targeting molecule forms a molecular barrier to initially inhibit platelet deposition and thrombus formation.[10] In addition, we can target therapeutic agents to specific vascular segments using a tag on the end of the polymer molecule. Using the protein-reactive PEG as described in our system permits modification of healthy endothelium or exposed matrix following vascular injury. This allows for the treatment of more conditions and is not dependent

upon the expression and availability of specific surface markers that are up-regulated in certain disease states, but still commonly found at various levels in healthy vasculature.

Still yet, sirolimus (CYPHER, Cordis J&J) and paclitaxel (TAXUS, Boston-Scientific) drug-eluting stents have demonstrated significant promise in preventing restenosis. Randomized-controlled trials have demonstrated a reduction in the need for repeat revascularization after coronary interventions by 60-80% when using drug-eluting stents.[31] However, long-term results of the effects of drug-eluting stents are still unknown and some complications and reservations have surfaced. As the drug-eluting stents are applied to more complex lesions, there have been increasing occurrences of late stent thrombosis.[32,33] The polymer substrate for delivery of the drug has also come under scrutiny. There are numerous reports suggesting a possible hypersensitivity reaction to the polymer coating on the stents resulting in extensive inflammation of the vessel wall.[32-34] Modification of injured vascular surfaces with our protein-reactive polymer provides another strategy that could even be used in conjunction with drug-eluting stents to further improve outcomes of coronary interventions.

In summary, this study demonstrates that a protein-reactive PEG can be used to modify healthy and injured vascular segments. Furthermore, this polymer can be used as a target for the site-specific delivery of microspheres to the labeled vascular tissue. Microspheres are representative of a particulate drug or carrier that could be loaded with various therapeutics designed to treat various ailments. In cases of vascular injury, such as with balloon angioplasties, carotid endarterectomies, or anastamoses, delivery of anti-thrombotics or anti-mitotics would assist in inhibiting restenosis. Additionally, since the protein reactive polymer modified healthy vasculature as well, it might be possible to label tumor vasculature for the targeted administration of chemotherapeutic agents.

ACKNOWLEDGEMENTS

Funding for this research was provided by the National Institutes of Health (grant # HL58617) and The National Tissue Engineering Center (log # 02059001). In addition, we would like to thank the animal surgical staff and monitors at the McGowan Institute for Regenerative Medicine that assisted with the *in vivo* studies. In particular, we would like to acknowledge Lisa Gordon and Aaron Dean who assisted with the surgical procedures and monitored the anesthesia for the animals.

REFERENCES

1. Arias E, Anderson RN, Kung HC, Murphy SL, Kochanek KD. Deaths: final data for 2001. *Natl Vital Stat Rep.* 2003;52:1-115.
2. Minino AM, Arias E, Kochanek KD, Murphy SL, Smith BL. Deaths: final data for 2000. *Natl Vital Stat Rep.* 2002;50:1-119.
3. Dzau VJ, Braun-Dullaeus RC, Sedding DG. Vascular proliferation and atherosclerosis: new perspectives and therapeutic strategies. *Nat Med.* 2002;8:1249-56.
4. Conde ID, Kleiman NS. Arterial thrombosis for the interventional cardiologist: from adhesion molecules and coagulation factors to clinical therapeutics. *Catheter Cardiovasc Interv.* 2003;60:236-46.
5. Garas SM, Huber P, Scott NA. Overview of therapies for prevention of restenosis after coronary interventions. *Pharmacol Ther.* 2001;92:165-78.
6. Welt FG, Rogers C. Inflammation and restenosis in the stent era. *Arterioscler Thromb Vasc Biol.* 2002;22:1769-76.

7. Savage MD, Mattson G, Desai S, Nielander GW, Morgensen S, Conklin EJ. *Avidin-Biotin Chemistry: A Handbook*. 2nd ed. Rockford: Pierce Chemical Company; 1994.

8. Roberts MJ, Bentley MD, Harris JM. Chemistry for peptide and protein PEGylation. *Adv Drug Deliv Rev*. 2002;54:459-76.

9. Harris JM. *Poly(ethylene glycol) chemistry : biotechnical and biomedical applications*. New York: Plenum Press; 1992.

10. Burchenal JE, Deible CR, Deglau TE, Russell AJ, Beckman EJ, Wagner WR. Polyethylene glycol diisocyanate decreases platelet deposition after balloon injury of rabbit femoral arteries. *J Thromb Thrombolysis*. 2002;13:27-33.

11. Deible CR, Beckman EJ, Russell AJ, Wagner WR. Creating molecular barriers to acute platelet deposition on damaged arteries with reactive polyethylene glycol. *J Biomed Mater Res*. 1998;41:251-6.

12. Huhtinen P, Soukka T, Lovgren T, Harma H. Immunoassay of total prostate-specific antigen using europium(III) nanoparticle labels and streptavidin-biotin technology. *J Immunol Methods*. 2004;294:111-22.

13. Hoya K, Guterman LR, Miskolczi L, Hopkins LN. A novel intravascular drug delivery method using endothelial biotinylation and avidin-biotin binding. *Drug Deliv*. 2001;8:215-22.

14. Zou J, Huang Y, Cao K, Yang G, Yin H, Len J, Hsieh TC, Wu JM. Effect of resveratrol on intimal hyperplasia after endothelial denudation in an experimental rabbit model. *Life Sci*. 2000;68:153-63.

15. Doornekamp FN, Borst C, Haudenschild CC, Post MJ. Fogarty and percutaneous transluminal coronary angioplasty balloon injury induce comparable damage to the arterial wall but lead to different healing responses. *J Vasc Surg.* 1996;24:843-50.

16. Barone GW, Farley PC, Conerly JM, Flanagan TL, Kron IL. Morphological and functional techniques for assessing endothelial integrity: the use of Evans blue dye, silver stains, and endothelial derived relaxing factor. *J Card Surg.* 1989;4:140-8.

17. Deible CR, Petrosko P, Johnson PC, Beckman EJ, Russell AJ, Wagner WR. Molecular barriers to biomaterial thrombosis by modification of surface proteins with polyethylene glycol. *Biomaterials.* 1999;20:101-9.

18. Thierry B, Winnik FM, Merhi Y, Tabrizian M. Nanocoatings onto arteries via layer-by-layer deposition: toward the in vivo repair of damaged blood vessels. *J Am Chem Soc.* 2003;125:7494-5.

19. Geho DH, Smith WI, Jr., Liotta LA, Roberts DD. Fibronectin-based masking molecule blocks platelet adhesion. *Bioconjug Chem.* 2003;14:703-6.

20. Hill-West JL, Chowdhury SM, Slepian MJ, Hubbell JA. Inhibition of thrombosis and intimal thickening by in situ photopolymerization of thin hydrogel barriers. *Proc Natl Acad Sci U S A.* 1994;91:5967-71.

21. West JL, Hubbell JA. Separation of the arterial wall from blood contact using hydrogel barriers reduces intimal thickening after balloon injury in the rat: the roles of medial and luminal factors in arterial healing. *Proc Natl Acad Sci U S A.* 1996;93:13188-93.

22. Tulis DA, Bohl Masters KS, Lipke EA, Schiesser RL, Evans AJ, Peyton KJ, Durante W, West JL, Schafer AI. YC-1-mediated vascular protection through inhibition of smooth

muscle cell proliferation and platelet function. *Biochem Biophys Res Commun.* 2002;291:1014-21.

23. Bohl KS, West JL. Nitric oxide-generating polymers reduce platelet adhesion and smooth muscle cell proliferation. *Biomaterials.* 2000;21:2273-8.

24. Alfke H, Wagner HJ, Calmer C, Klose KJ. Local intravascular drug delivery: in vitro comparison of three catheter systems. *Cardiovasc Intervent Radiol.* 1998;21:50-6.

25. Du X, Yang Y, Le Visage C, Chen HH, DeJong R, Qiu B, Wang D, Leong KW, Hamper UM, Yang X. In vivo US monitoring of catheter-based vascular delivery of gene microspheres in pigs: feasibility. *Radiology.* 2003;228:555-9.

26. Yang X. Imaging of vascular gene therapy. *Radiology.* 2003;228:36-49.

27. Moon MC, Molnar K, Yau L, Zahradka P. Perivascular delivery of losartan with surgical fibrin glue prevents neointimal hyperplasia after arterial injury. *J Vasc Surg.* 2004;40:130-7.

28. Thomas AC, Campbell JH. Targeted delivery of heparin and LMWH using a fibrin antibody prevents restenosis. *Atherosclerosis.* 2004;176:73-81.

29. Yun YH, Goetz DJ, Yellen P, Chen W. Hyaluronan microspheres for sustained gene delivery and site-specific targeting. *Biomaterials.* 2004;25:147-57.

30. Sakhalkar HS, Dalal MK, Salem AK, Ansari R, Fu J, Kiani MF, Kurjiaka DT, Hanes J, Shakesheff KM, Goetz DJ. Leukocyte-inspired biodegradable particles that selectively and avidly adhere to inflamed endothelium in vitro and in vivo. *Proc Natl Acad Sci U S A.* 2003;100:15895-900.

31. Hodgson JM, Bottner RK, Klein LW, Walpole HT, Jr., Cohen DJ, Cutlip DE, Fenninger RB, Firth BG, Greenberg D, Kalisky I, Meskan T, Powell W, Stone GW, Zito JP, Clark

MA. Drug-eluting stent task force: final report and recommendations of the working committees on cost-effectiveness/economics, access to care, and medicolegal issues. *Catheter Cardiovasc Interv*. 2004;62:1-17.

32. Virmani R, Farb A, Guagliumi G, Kolodgie FD. Drug-eluting stents: caution and concerns for long-term outcome. *Coron Artery Dis*. 2004;15:313-8.

33. Bhatia V, Bhatia R, Dhindsa M. Drug-eluting stents: new era and new concerns. *Postgrad Med J*. 2004;80:13-8.

34. Mitka M. Drug-eluting stents show promise: but experts warn against enthusiasm outpacing science. *Jama*. 2004;291:682-3.

Figure 1.

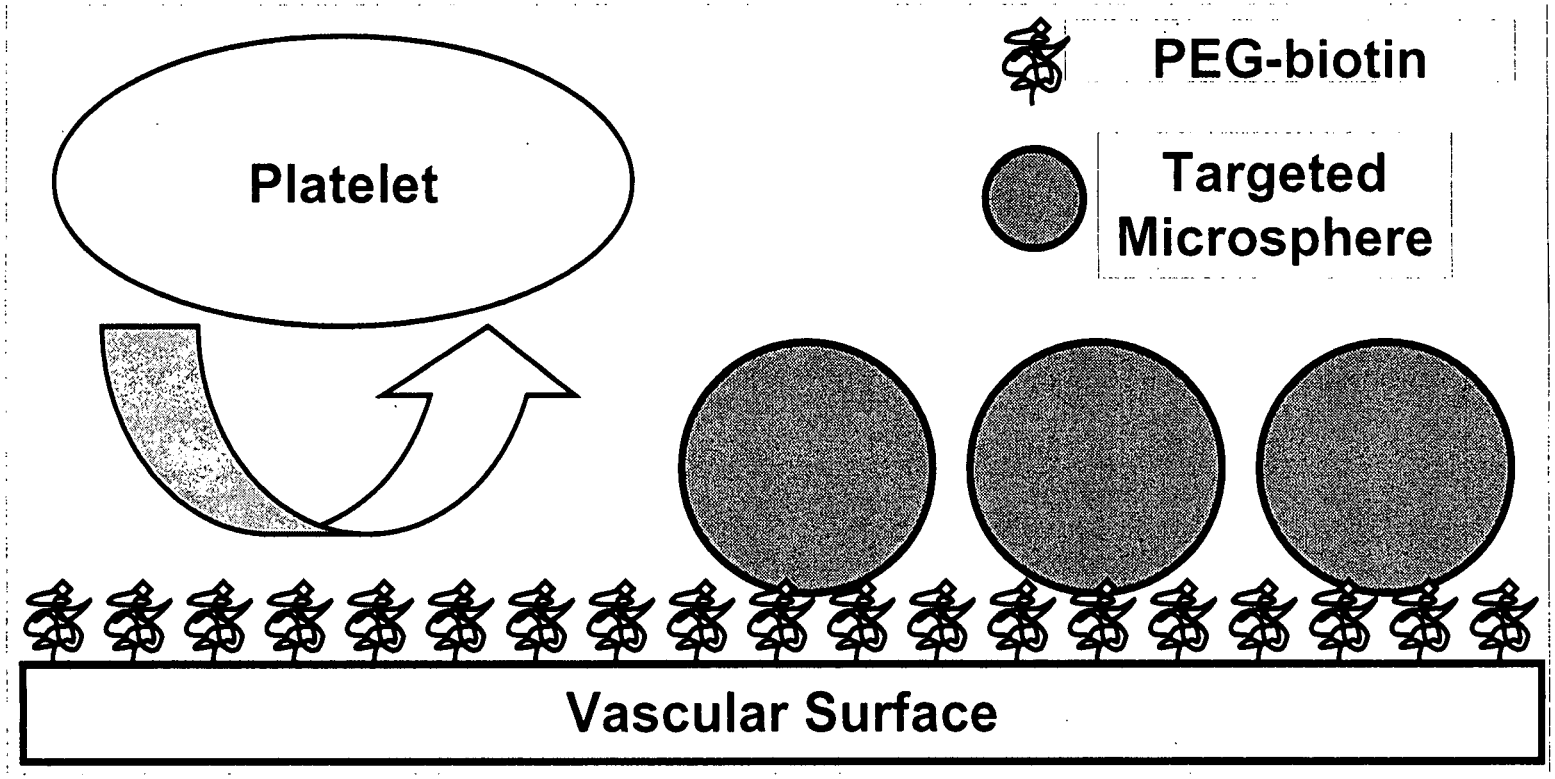
PEG-biotin
Platelet
Targeted
Microsphere
Vascular Surface

Figure 2.

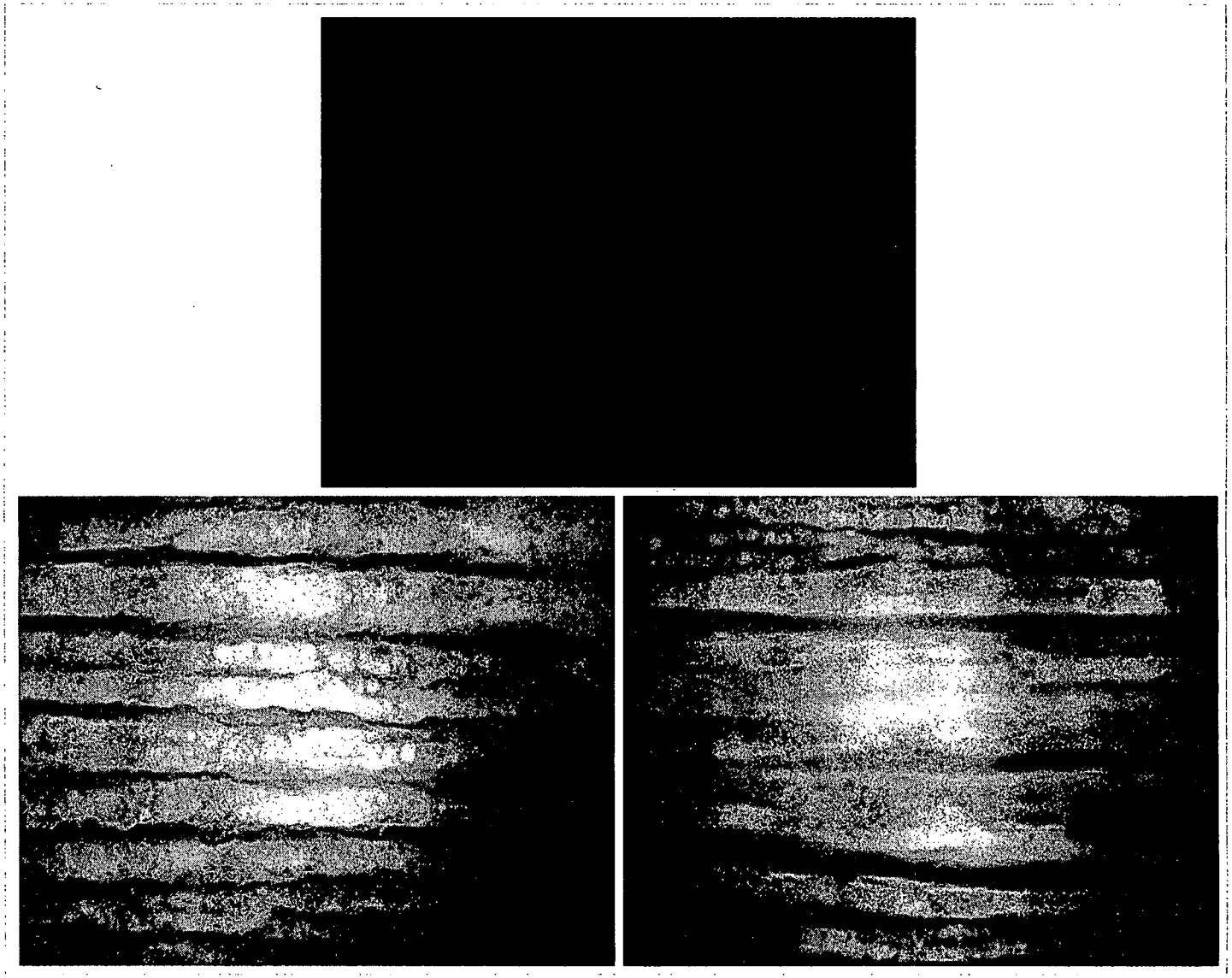

Figure 3.

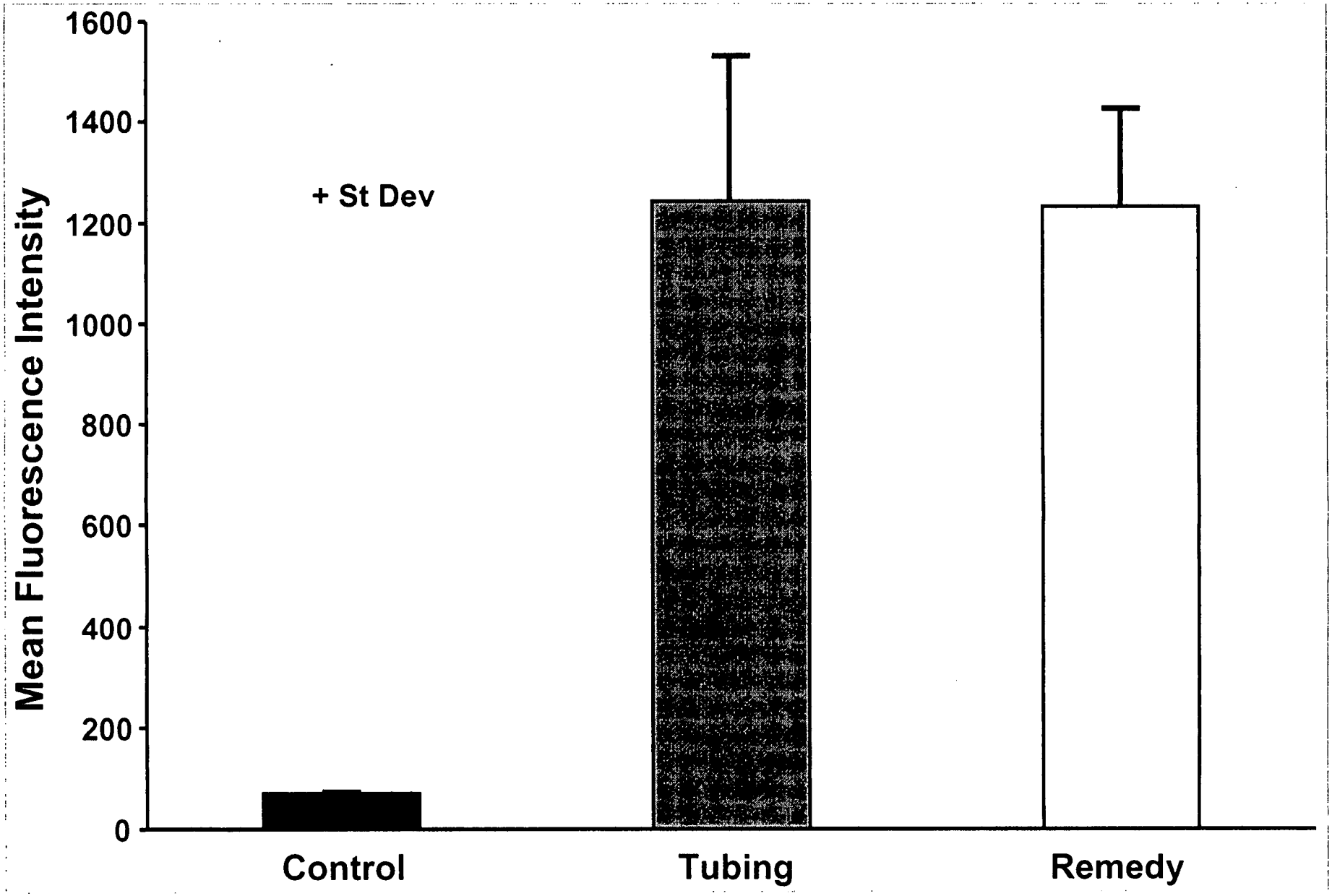
Mean Fluorescence Intensity
1600
1400
1200
1000
800
600
400
200
0
+ St Dev
Control
Tubing
Remedy

Figure 4.

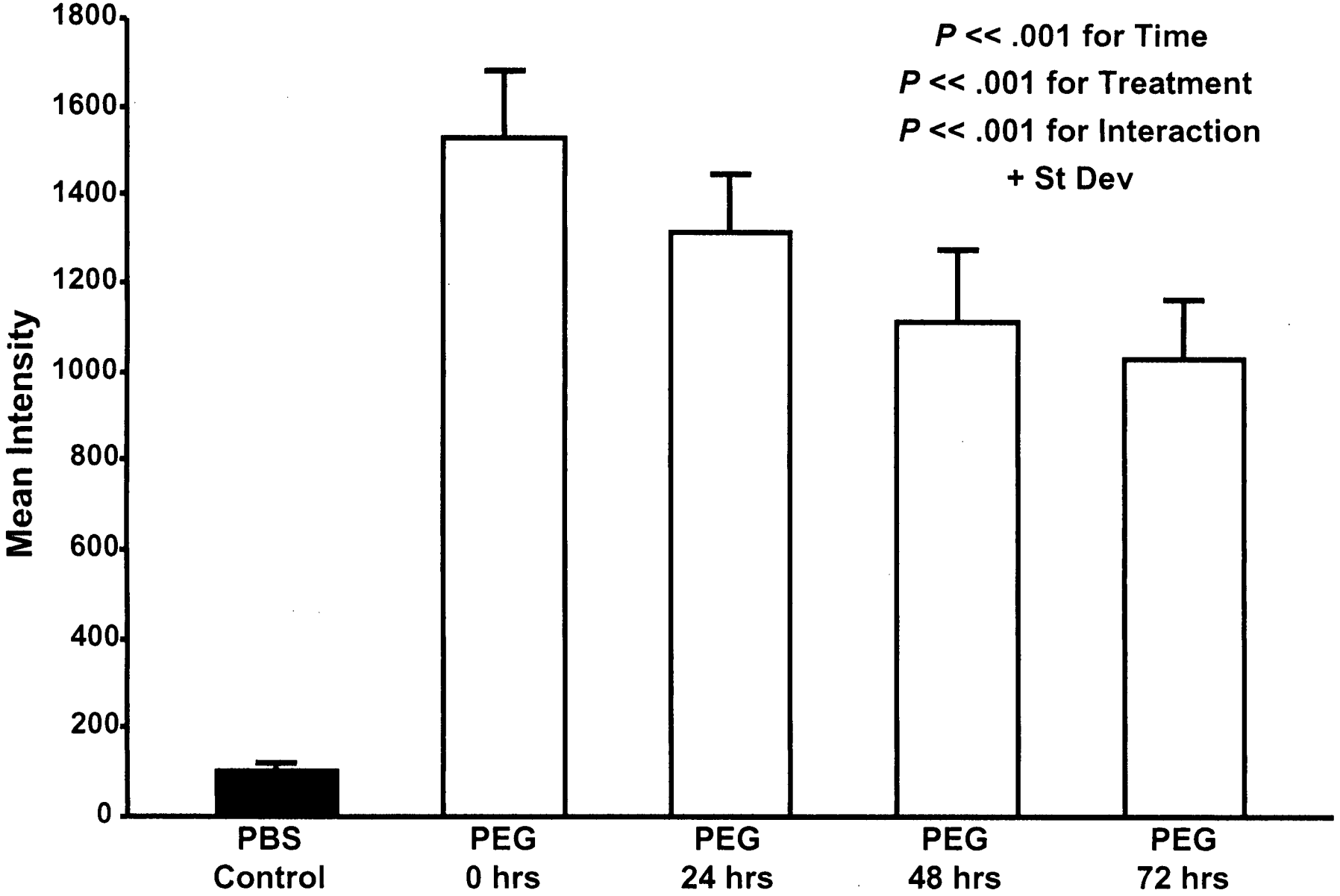
1800
1600
1400
1200
1000
800
600
400
200
0
Mean Intensity
P << .001 for Time
P << .001 for Treatment
P << .001 for Interaction
+ St Dev
PBS Control
PEG 0 hrs
PEG 24 hrs
PEG 48 hrs
PEG 72 hrs

Figure 5.

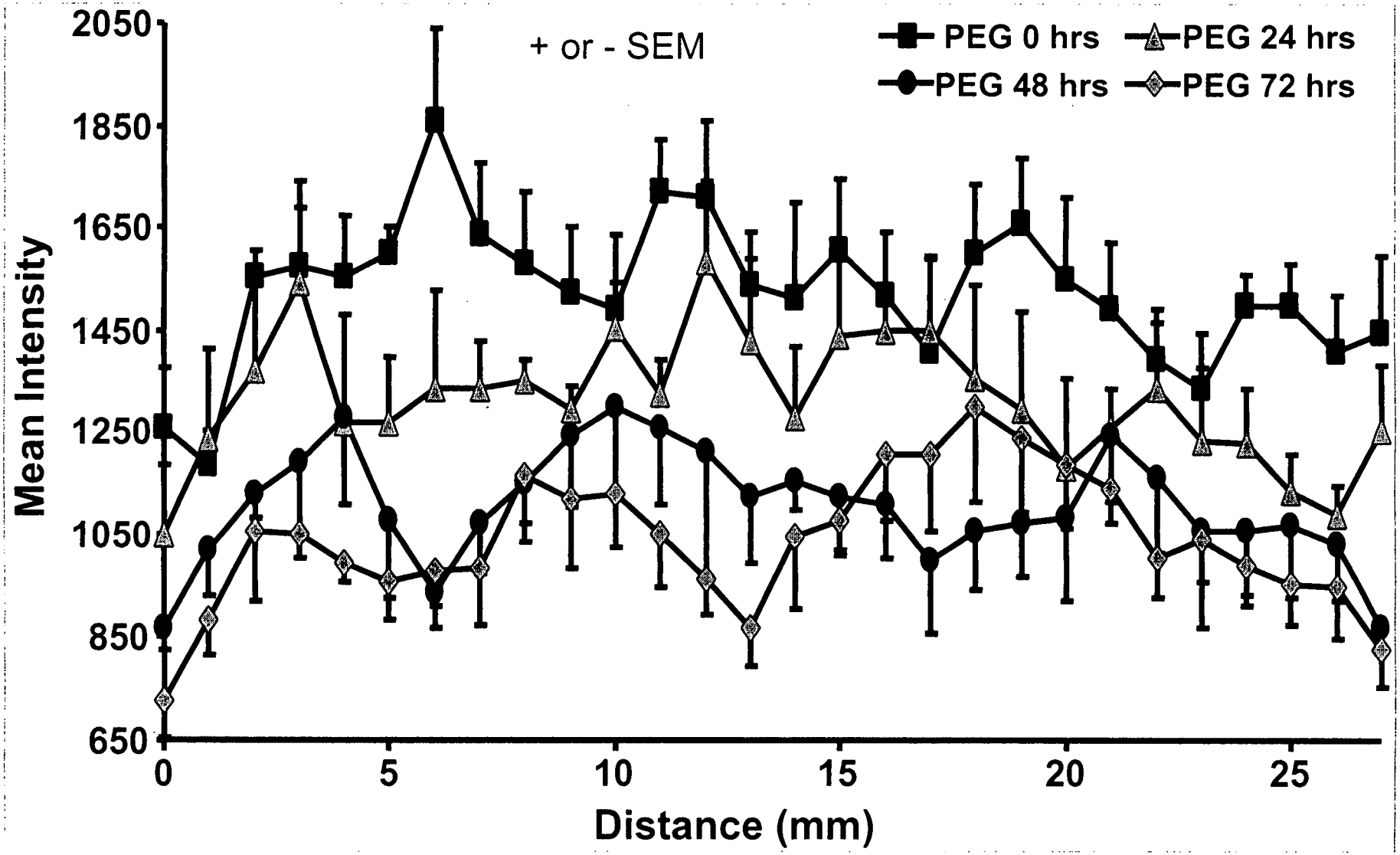
+ or - SEM
PEG 0 hrs
PEG 24 hrs
PEG 48 hrs
PEG 72 hrs
Mean Intensity
2050
1850
1650
1450
1250
1050
850
650
0
5
10
15
20
25
Distance (mm)

Figure 6.

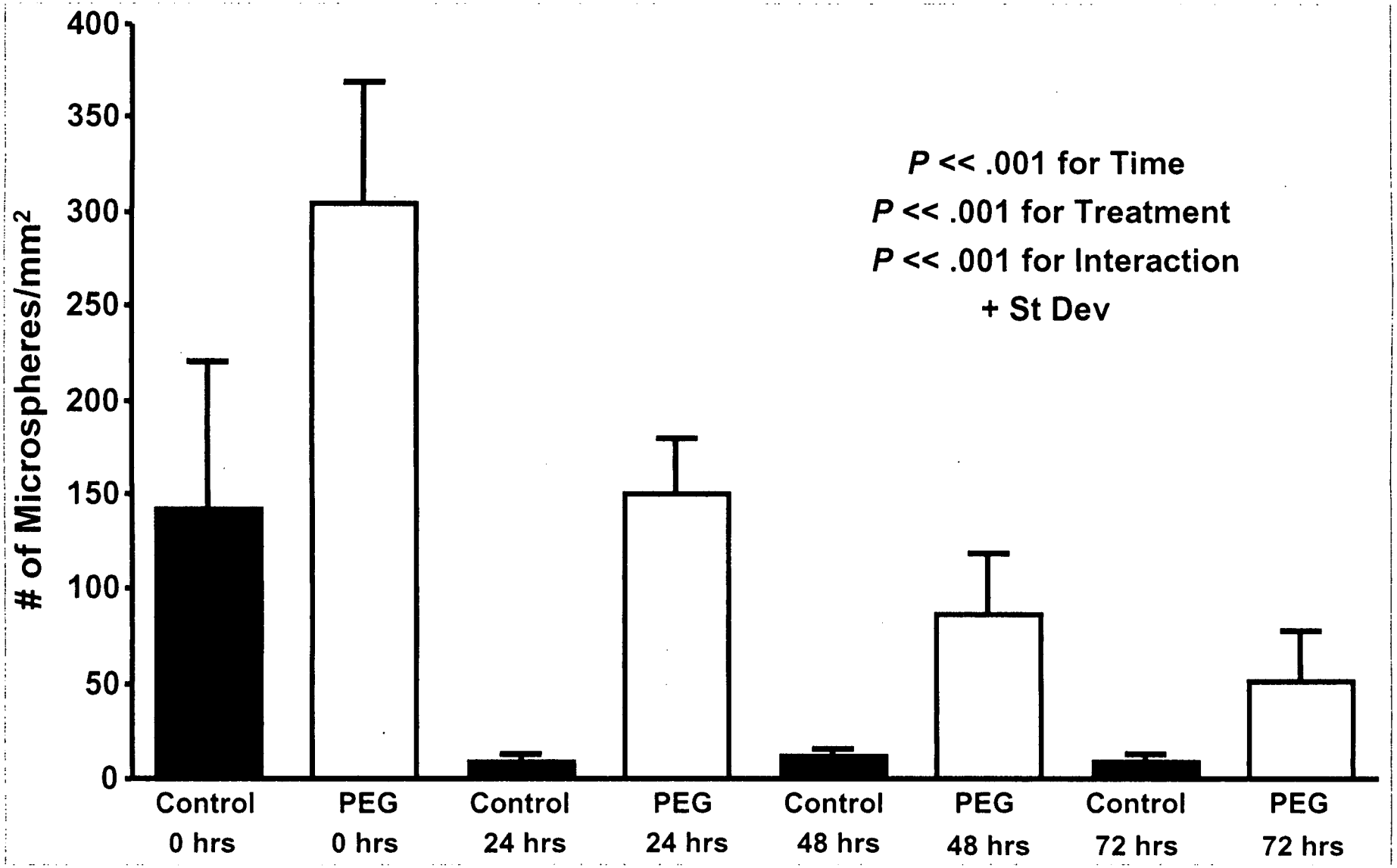
400
350
300
250
200
150
100
50
0
# of Microspheres/mm²
P << .001 for Time
P << .001 for Treatment
P << .001 for Interaction
+ St Dev
Control 0 hrs
PEG 0 hrs
Control 24 hrs
PEG 24 hrs
Control 48 hrs
PEG 48 hrs
Control 72 hrs
PEG 72 hrs

Figure 7.

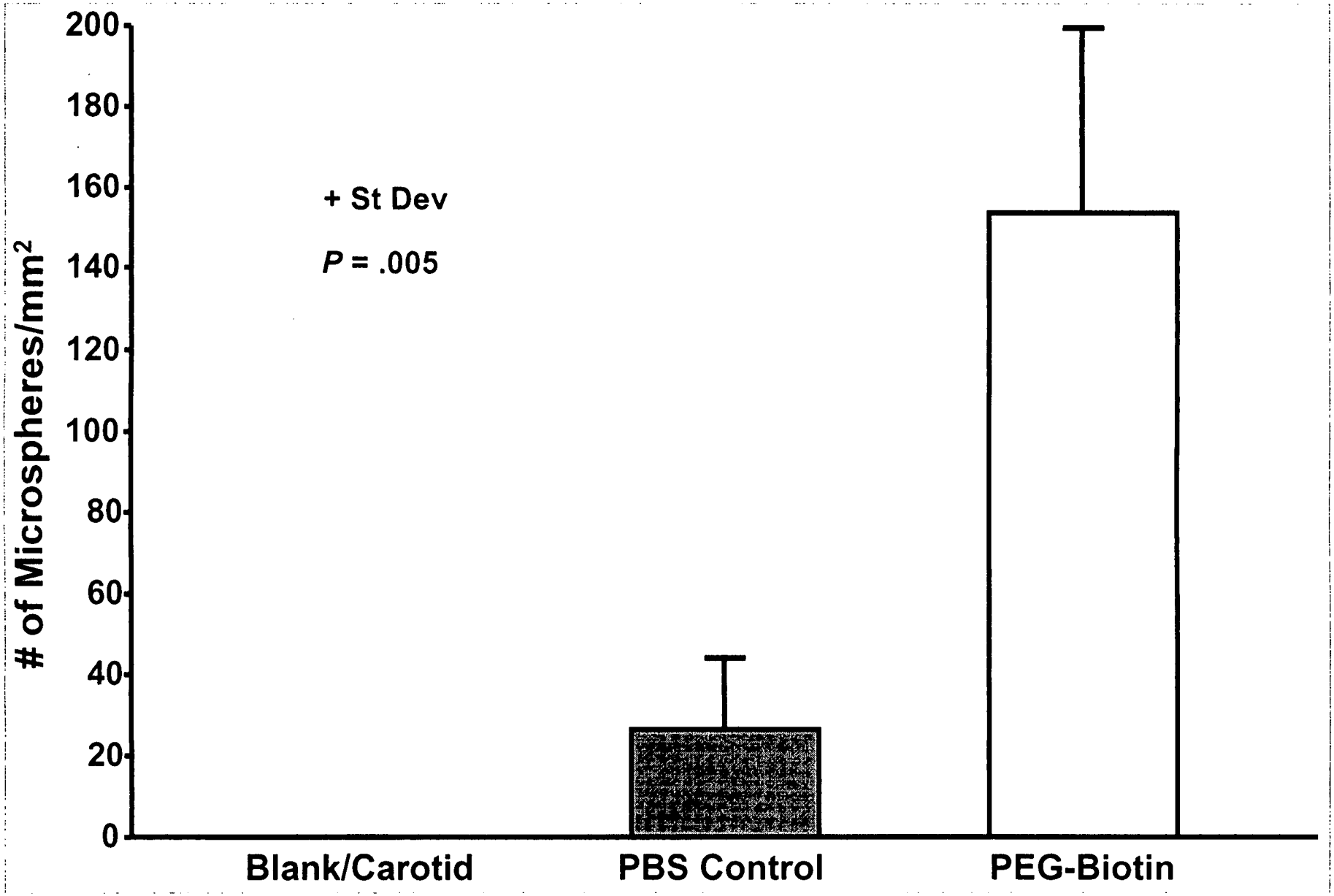
200
180
160
140
120
100
80
60
40
20
0
# of Microspheres/mm2
+ St Dev
P = .005
Blank/Carotid
PBS Control
PEG-Biotin

FIGURE LEGENDS

Figure 1. Schematic of the proposed targeted delivery system. The reactive polymer is covalently attached to the vascular surface forming a molecular barrier, inhibiting platelet and leukocyte adhesion. Targeted microspheres or cells will specifically adhere to vascular surfaces labeled with the polymer.

Figure 2. Fluorescent micrographs of different techniques to modify balloon injured vessels with reactive PEG-fluorescein: (A) Vehicle (PBS) control, (B) Micro-Renathane tubing, (C) Remedy channeled drug delivery balloon catheter. Scale bar is 100 μm.

Figure 3. Mean fluorescence intensity comparing the vehicle, Micro-Renathane tubing, and Remedy channeled drug delivery balloon catheter delivery methods. Data is shown as MESF +St Dev.

Figure 4. Duration of PEG-fluorescein on balloon injured rabbit femoral arteries after modification at 0, 24, 48, and 72 hrs. Data is shown as MESF +St Dev with $n = 4$ at all times and treatments and the results are significant with $p << .001$ for the time, treatment, and interaction.

Figure 5. Distribution of PEG-fluorescein modified, balloon injured rabbit femoral arteries along the vessel length at 0, 24, 48, and 72 hrs. Data is shown as MESF +/-SEM.

Figure 6. Number of targeted microspheres adhering to control and PEG-biotin treated, balloon injured rabbit femoral arteries in vivo at 0, 24, 48, and 72 hrs post-modification. Data is shown +St Dev with n = 4 at all times and treatments and the results are significant with $p << .001$ for the delivery time, treatment, and interaction.

Figure 7. Number of targeted microspheres adhering to control and PEG-biotin treated healthy rabbit endothelium in vivo at 0 hrs. Data is shown +St Dev and the results are significant with $P = .005$.